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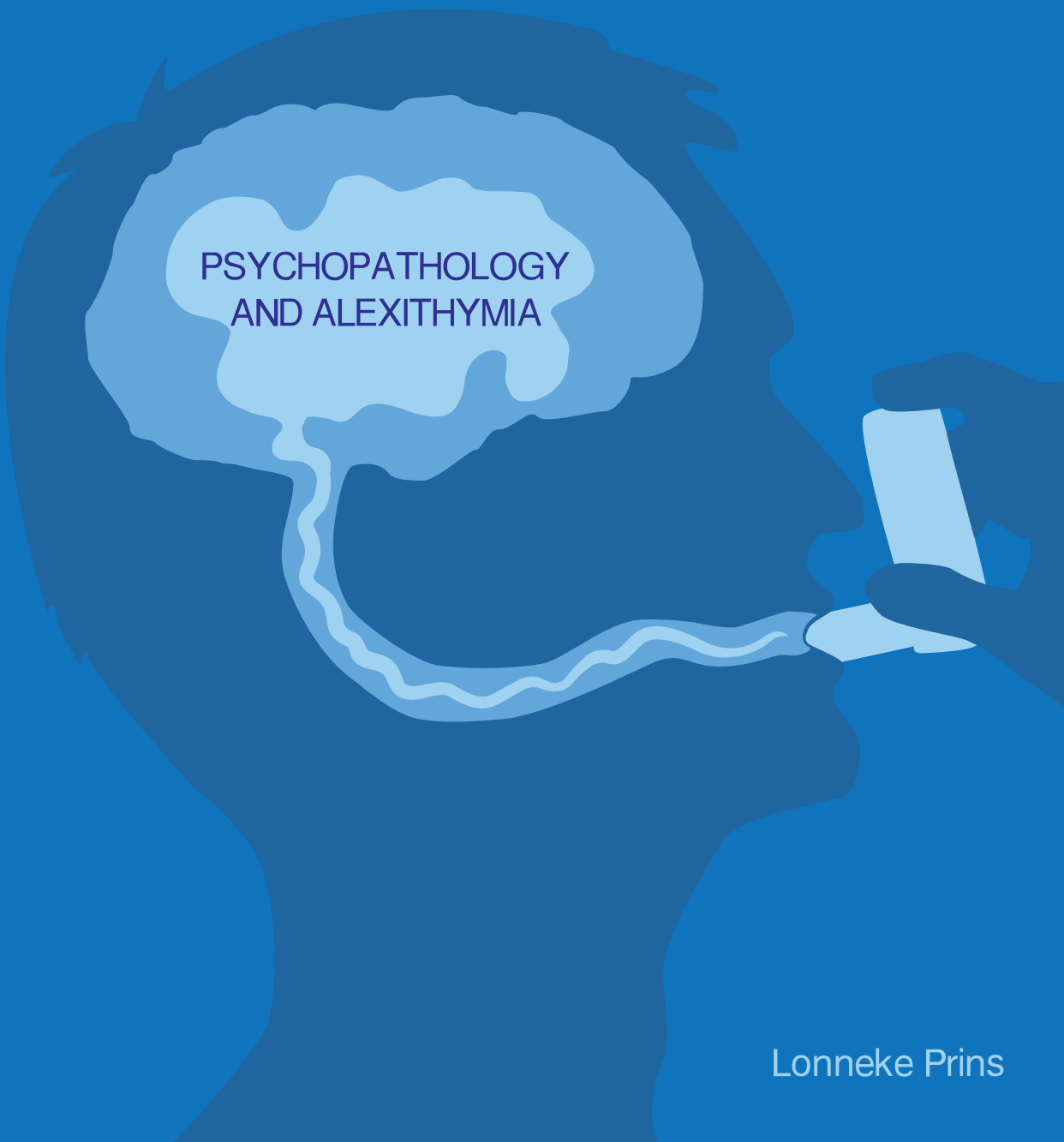

Lonneke Prins

A PSYCHOLOGICAL PERSPECTIVE ON DIFFICULT ASTHMA IN ADULTS

PSYCHOPATHOLOGY AND ALEXITHYMIA

Lonneke Caroline Janine Kanters-Prins

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PSYCHOPATHOLOGY AND ALEXITHYMIA

PROEFSCHRIFT

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General introduction

GENERAL INTRODUCTION

Asthma and difficult asthma

Asthma is a heterogeneous disease in which patients have a history of respiratory symptoms, such as wheezing, shortness of breath, chest tightness and cough that vary over time and intensity and with variable expiratory airflow limitation (variable lung function) [1]. Asthma itself is characterized by airway obstruction, airway inflammation and bronchial hyper responsiveness [2]. An estimated 300 million children and adults are affected by asthma worldwide. Although asthma is now a well treatable disease, its incidence is increasing over the years, making it still a major and increasing health problem for society [1]. To improve awareness, prevention and management of asthma worldwide, The Global Initiative for Asthma (GINA) was established in 1993 [1]. This initiative resulted in an improved guideline for treatment of asthma that can be used worldwide and adapted to individual needs of patients with asthma [1]. GINA published this guideline, The Global Strategy for Asthma and Prevention, which was revised in 2014 and updated in 2015.

GINA [1] first recommends assessing asthma control, treatment issues like adherence, avoidance of allergens and inhaler technique and the assessment of comorbid somatic and psychiatric symptoms and diseases. Second, GINA recommends, assessing severity of asthma symptoms by the level of treatment that is required to control symptoms and exacerbations. Appropriate control of disease for patients is described as the absence of troublesome symptoms during day and night, patients are in need of little or no reliever medication, have productive physically active lives, have normal or near normal lung function and are able to avoid serious asthma exacerbations. When the airways become inflamed which causes asthma symptoms by restricting or limiting the airflow to and from the lungs and results in decreased lung function and exacerbations, asthma is not under control.

GINA guidelines recommend a stepwise approach of five steps of pharmacological treatment to achieve and maintain control over the disease [1]. In the first three steps low doses of inhaled corticosteroids are preferred in combination with short-acting beta$_2$-agonist (SABA). At step four and five additional treatment with long acting beta$_2$-agonist (LABA), Anti-IgE and/or oral corticosteroids are advocated. This pharmacological treatment is adjusted by stepping down or up according to asthma control.

Most patients are treated well according to these guidelines and achieve control over asthma symptoms. About 5% of asthma patients do not achieve optimal control and pose a substantial health problem for society. In the US 1,25 million asthma patients [3] and 22 000 asthma patients in The Netherlands [4] cannot control their disease and consume a substantial part of the overall cost of asthma [5-8]. In addition, these patients are often extremely invalidated by their symptoms influencing both their daily life but also resulting in severe exacerbations and thus hospitalisations [6, 9-10]. Their asthma symptoms are not temporarily but chronically poor controlled which causes low quality of life [11]. Moreover, these patients are at risk of complications related to use of (high) doses of oral steroids [12], lung damage, their condition can be life threatening and also cause extreme anxiety [13].

This thesis mainly focuses on this difficult-to-treat patient group with asthma, i.e. specifically adult patients with difficult asthma (DA). Adult patients with difficult-to-treat asthma in this thesis are referred to as patients with difficult asthma (DA) only if, according to GINA guidelines, these patients do not achieve control at step 4 or 5 of GINA guidelines [1, 14]. This patient group constitutes a heterogeneous group with different subgroups of patients such as brittle asthma, and near fatal asthma [15, 16]. These are all subgroups with asthma with extreme difficult to control asthma symptoms. Specifically, in near fatal asthma, patients suffer from near fatal attacks that comprise of a disproportionate part of asthma morbidity [17].
The combination of the relatively low prevalence, heterogeneity and a definition that is based on pharmacological treatment makes DA an asthma population that is not only difficult-to-treat but also difficult to study. A better understanding of DA in order to create a basis for developing more adequate treatment opportunities is therefore the main aim of this thesis.

A psychological approach in understanding difficult asthma

A *pathophysiological* approach has -as by default- been the first choice in studying and treating DA, resulting however in an outcome which is far from optimal. This thesis focuses on a *psychological* approach to DA -along with a pathophysiological approach- that may contribute to a better understanding of patients with DA and may constitute as such a better approach for an improved treatment. A psychological approach is the more relevant as the origin of 'difficult' asthma does not appear to be solely related to pure pathophysiological processes for all patients; some patients with DA do have severe bronchoconstriction

during exacerbation of their asthma while other patients during an exacerbation have no or negligible bronchoconstriction [18]. A psychological approach to DA is a point of view that corresponds with contemporary views of the role of psychological factors in chronical physical illness such as cardiovascular diseases [19]. It implies a question whether a pathophysiological approach is as self-evident as it appears.

In analogy with these other chronic medical conditions, it is especially interesting to study whether a psychological approach –or even better: a multidisciplinary approach- could improve the available knowledge in understanding the uncontrollability of asthma symptoms and therefore the severe and frequent exacerbations in DA.

In this thesis we focus first on co-morbid psychopathology, at both symptom and syndrome level and second on alexithymia –the inability to give words to emotions [20]- which are both probable factors that may contribute to the uncontrollability of asthma and therefore of the existence of DA. Psychopathology is a well-known concept in asthma while alexithymia seems to be a relatively new concept in asthma. Both lack empirical evidence in whether and how they are possibly related to DA.

Psychopathology

There is a difference between psychiatric symptoms and psychiatric syndromes. Psychiatric syndromes refer to a specific set of symptoms and course and can be diagnosed adequately (with a semi-structured interview) by trained professionals. Psychiatric symptomatology may also be assessed by self-report questionnaires, as is often the case in research. The main difference between psychopathology at symptom level compared to syndrome level is first that a syndrome comprises of a combination of symptoms -often related to each other-, second the duration of symptoms is often long and of a specific minimal duration and third the impact of these symptoms on daily life have to be significant. As these syndromes each represent a multitude of symptoms one may deduce that the presence of a psychiatric syndrome may complicate asthma in a more severe and/or complicated way.

The prevalence of psychiatric syndromes in asthma is estimated at 31% [21], which is high compared to the overall prevalence of psychiatric syndromes (18%) in The Netherlands [22]. There is worldwide consensus that psychiatric symptoms like anxiety and depression are important complicating factors in asthma [23]. GINA guidelines [1] advise psychiatric symptoms to be screened for in patients with asthma in an early stage by their GPs and pulmonologists. Psychiatric

symptoms are known to have a negative impact in patients with asthma on adequate medication use, exacerbations and patients' perceived wellbeing and vice versa asthma symptoms negatively influence psychiatric symptoms [24-27]. The specific nature of the relation between psychiatric symptomatology and asthma is unclear, i.e. whether asthma or psychiatric symptoms are cause or consequence, however the relationship is probably bi-directional [28, 29]. Specifically anxiety and panic, for instance, may directly exacerbate symptoms by hyperventilation [30]. And the severity of asthma symptoms may also cause extreme anxiety and thus psychiatric symptomatology [31].

Until now research on psychopathology in *asthma in general* has been scarce and has mostly focused on psychiatric symptoms with the screening of self-report questionnaires. Studies on psychiatric syndromes in asthma –to be diagnosed by specific structured interviews and observation- are much scarcer and have thus far mainly focused on anxiety and affective disorders, specifically post traumatic stress disorder (PTSD) [32-38]. Asthma has also been associated with alcohol/substance abuse and somatoform disorders [39]. Only one study [40] examined the prevalence of personality disorders in a population of asthma patients, which proved to be similar to the prevalence in the general population. The relationship between severity of asthma and psychopathology yields different results in different studies [2, 41-43], probably because of use of different instruments and heterogeneity of patients.
Research on *psychopathology* (both at syndrome as well as symptom level) in DA is scarce. As a consequence it is unclear whether patients with severe asthma like DA present with high levels of psychopathology. It seems plausible that psychopathology is important in DA. Psychopathology is seen as a contributing factor in DA [18] although empirical evidence seems lacking. Knowledge concerning psychopathology in DA should be further developed, as it may constitute a significant factor in the development and existence of DA. Therefore research on psychiatric symptoms and syndromes in DA is necessary; it may provide us with a better understanding of DA and may provide opportunities in diagnostics and treatment if psychiatric symptoms and/or syndromes are indeed highly prevalent in DA and if it influences health related wellbeing in patients.

Alexithymia

A less known and less studied concept that may also influence the uncontrollability of asthma symptoms in chronic conditions is alexithymia. Clinical practice and the existing management protocols for treating asthma, mention alexithymia

as a contributing concept in DA (44). However, also for alexithymia, empirical evidence seems lacking.

Literally alexithymia means without words for emotions [20]. It consists of four aspects: (1) difficulty identifying and describing feelings; (2) difficulty distinguishing feelings from bodily sensations; (3) reduction or absence of symbolic thinking; (4) utilitarian thinking without fantasy [45, 46]. Alexithymia is a dimensional concept that can be present from low negligible to high levels [46]. Patients with asthma are assumed to have high levels of alexithymia [45]. Alexithymia seems an important construct in asthma because patients with asthma need to be able to distinguish between feelings and bodily sensations [1]. Moreover, the emotional response to asthma symptoms defines the tendency to seek care and take medication [47]. Alexithymia can be regarded as an impairment that may lead on the one hand to the misinterpretation/ misperception of physical symptoms. On the other hand, alexithymia tends to influence illness perception and can lead to the overreporting and catastrophizing of somatic sensations. Both tendencies may result in poor asthma management [48].

Often overperception or blunted perception of symptoms occurs in patients with asthma [49]. Overperception or blunted perception occurs when the experience of dyspnea and of pathophysiological lung function does not correspond. Dyspnea or breathlessness is a subjective experience in which not pathophysiological but psychological factors and situational factors explain most of its variance [50]. In literature, patients with asthma are arranged in three categories according to the difference between dyspnea and lung function: normoperceivers, hypoperceivers and hyperperceivers [51]. In normoperceivers a marginal difference between dyspnea and lung function is seen. In hypoperceivers, however, there is blunted perception of symptoms, which can delay help seeking and lead to inadequate utilization of medication. Moreover, hypoperception is a potential risk factor for severe exacerbations [52] and can even lead to (avoidable) death. Instead of blunted perception, hyperperceivers are characterized by overperception of symptoms: More symptoms are reported than medically can be explained. This can lead to overutilization of health care and to iatrogenic side effects [53].

Alexithymia is on the one hand an old concept in asthma. On the other hand alexithymia did not evolve in asthma literature as it certainly did in other chronic somatic diseases. Recent studies in other somatic diseases such as diabetes and coronary heart disease show that not only alexithymia can be improved during treatment but also that patients with reduced alexithymia scores after

treatment have better somatic treatment outcomes that last over two years [54]. This could also imply treatment opportunities for patients with asthma, specifically DA.
Since alexithymia is hardly studied in asthma it is important to first review which knowledge is already available on alexithymia in asthma and specifically DA

Specialised pulmonary rehabilitation

A psychological approach –along with pathophysiological approach -to DA can possibly create better treatment opportunities. It is however also interesting whether patients with DA benefit from the existing treatment opportunities and whether psychiatric symptomatology complicates treatment and influences perceived wellbeing in DA or not.
Treatment of asthma is, in general, provided by the general practitioner (GP) in a Primary Care setting. The GP can provide treatment according to GINA guidelines. However, if after 3-6 months at step 4 patients do not achieve control over asthma symptoms, if asthma symptoms are too severe or if there are doubts about diagnosis at an earlier step, referral to a pulmonologist is recommended besides stepping up in treatment [1]. The latter can – in case of poor treatment response – refer to an asthma rehabilitation centre [1]. Before referral to a specialised rehabilitation centre usually outpatient rehabilitation in a general hospital setting is prescribed unless asthma symptoms are too severe or if there are doubts about diagnosis.
The American Thoracic Society (ATS) and (European Respiratory Society (ERS) have adopted the following definition of pulmonary rehabilitation: "Pulmonary rehabilitation is an evidence-based, multidisciplinary, and comprehensive intervention for patients with chronic respiratory diseases who are symptomatic and often have decreased daily life activities. Integrated into the individualized treatment of the patient, pulmonary rehabilitation is designed to reduce symptoms, optimize functional status, increase participation, and reduce health care costs through stabilizing or reversing systemic manifestations of the disease." [55, page e14]. Existing pulmonary rehabilitation programmes in The Netherlands vary considerably in setting, intensity, content and duration. Most of these rehabilitation programmes are outpatient programmes along intensive inpatient programmes.
Specifically specialised pulmonary rehabilitation programmes generally provide a scrupulous multidisciplinary assessment involving assessment of both somatic and psychosocial problems and their interaction over 4 days. Patients attending the rehabilitation have to be abstinent from smoking during rehabilitation.

Exclusion criteria for participation in the programme are also all disorders and diseases, both physical and psychiatric, that prevents a patient to participate in the treatment programme [56]. Specialised pulmonary rehabilitation is mostly inpatient.
The most rigorous specialised pulmonary rehabilitation comprises a multidisciplinary inpatient programme of 3-months by a team of healthcare professionals, consisting of pulmonary physicians, specialized health care psychologists, respiratory nurses, physiotherapists, exercise therapists, dieticians, social workers, therapeutic recreation specialists and occupational therapists [55]. The rehabilitation centres offer a programme of 20-25 hours a week that is highly individualized with also group-based psychosocial counseling sessions [56]. The program further consists of exercise training, education, and optimization of medication. Specialized health care psychologists treat psychiatric symptoms and syndromes during the programme. If necessary, patients can be referred to more intensive treatment for psychiatric symptoms or syndromes before or after the programme.

The goal of the rehabilitation is to reduce symptoms, decrease disability and improve health related perceived wellbeing [55]. The goal is hence also to reduce exacerbations and hospitalizations. Interventions during the programme are targeted at both primary and secondary impairments of asthma, i.e. targeted at the direct and indirect impairments of asthma. However studies on the viability and outcome of these programmes for DA patients, specifically at longitudinal follow up, are very scarce.
As viability and outcome till now have not been systematically studied for patients with DA, further research and insight in therapeutic factors in such a rehabilation programme might contribute to optimal development of such programmes.

AIMS AND OUTLINE OF THE THESIS

The main aim of this thesis was a better understanding of DA in order to create a basis for developing more adequate treatment opportunities from a psychological point of view. The existing recommendations for treating DA by GINA criteria incorporate a psychological point of view, however empirical support seems scarce. In addition, some patients still remain difficult-to-treat [1]. Two concepts that are considered complicating factors in asthma in both worldwide guidelines and clinical practice are psychiatric symptomatology /

syndromes and alexithymia. **Chapter 2**, reports a review of studies on psychiatric symptomatology in DA evaluating the available empirical literature. In **Chapter 3** the level of psychiatric symptomatology was studied in patients with DA along with the question if there is a relation with perceived wellbeing. Subsequently in **Chapter 4**, we specifically studied the prevalence of both major mental psychiatric disorders and personality disorders in DA. To generate more insight in a possible role of alexithymia in DA we first reviewed in **Chapter 5** studies on the prevalence of alexithymia in asthma in general. Second, we reviewed studies on possible associations between alexithymia and severity of asthma, asthma control and quality of life. Third, we reviewed the studies on treatment and treatment outcome of alexithymia in asthma. We then studied in **Chapter 6** whether patients with DA could benefit from existent specialized pulmonary rehabilitation programmes with a special focus on psychiatric symptomatology. We therefore first evaluated whether psychiatric symptoms in patients with DA do change during specialised pulmonary rehabilitation. Second, we assessed whether there was an association between psychiatric symptoms and a possible benefit during the specialized pulmonary rehabilitation on health related wellbeing. Third, we evaluated whether a possible benefit of specialised pulmonary rehabilitation persists at longitudinal follow-up.
Finally, **Chapter 7** concludes with the main findings and a general discussion of this thesis. Specifically we will discuss suggestions to create better treatment opportunities for patients with DA from a psychological point of view in relation to the results of the current thesis.

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Chapter 2

Psychopathology in difficult asthma

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ABSTRACT

Objective: Within the asthma population, difficult asthma (DA) is a severe condition in which patients present with frequent exacerbations, hospitalizations and emergency room visits. The identification and treatment of psychopathology is included in the management of DA. Psychopathology is supposed to predispose patients to DA or vice versa; psychopathology may develop as a consequence of DA. We reviewed the available literature on empirical findings regarding psychopathology in adult patients with DA.

Methods: Studies in English language journals using MEDLINE, Cochrane and PsycINFO databases, were retrieved by an electronic search published from 1990 till July 2014.

Results: Literature on psychopathology in DA is scarce. The search identified 16 articles of which only 6 articles were specifically about psychopathology in adult patients with DA. Almost half of the patients with DA had evidence of psychopathology at both syndrome and symptom level. Moreover, psychopathology appeared to be related to frequent exacerbations in patients with DA.

Conclusions: This literature review suggests a high prevalence of psychopathology of patients with DA, although it remains unclear whether psychopathology occurs more often in DA compared to ''stable asthma''. More research is needed on a possible role of psychopathology on clinical signs and symptoms in DA.

INTRODUCTION

Asthma is a respiratory disease characterized by airway obstruction, airway inflammation and bronchial hyper responsiveness [1,2]. Asthma is a common and increasing problem in our society [2,3]. About 8% of the adult population in Europe, North America and Australia has asthma [4]. Asthma can be a life-threatening condition although usually, asthma is well controlled with standard treatment. Standard treatment is directed at maximizing the symptom-free periods and keeping the airways in the best possible physical state [2–4].

Treatment mostly involves the prescription of medication, avoiding asthma triggers and improving self-management strategies. Recent guidelines classify severity based on responsiveness to treatment [2,5]. Approximately 5% of patients with asthma have difficult asthma (DA) [6], as defined by the European Respiratory Society (ERS) task force [7], i.e. these patients do not reach an acceptable level of control at step 4 or 5 of prescribed treatment [3]. DA is defined as a failure to reduce the clinical manifestation of asthma symptoms despite maximal treatment [8–10]. As a result patients with DA have frequent exacerbations, hospital admissions and emergency room (ER) visits [8–10]. Patients with DA form a heterogeneous group with ''uncontrollable symptoms''. DA includes clinical subgroups with refractory asthma, near fatal asthma (NFA) [11], brittle asthma, nocturnal asthma, corticosteroid-resistant asthma, corticosteroid-dependent asthma and therapy-resistant asthma [6].

Although DA consists of a small group of patients, the impact on healthcare is significant. A substantial part of the overall costs of asthma is consumed by patients with DA because of the many hospitalizations, ER visits and high medication use [3,8,12,13]. Moreover, DA influences the quality of life of patients themselves as well as their environment [8]. Ultimately DA can even lead to death. Reasons why asthma symptoms in these patients are difficult to manage are not well understood [3]. Management programs concerning the treatment of DA propose a stepwise management of the disease [6,14]. One step in the treatment of DA is the modification of socioeconomic factors influencing disease control and the identification and treatment of psychopathology, mental disorders as defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) [15], the standard classification used by mental health professionals. Psychopathology is suggested to obscure diagnostics and to complicate the treatment of asthma [14].

In the asthma population, the prevalence of psychopathology is significantly higher compared to the general population [16–18], both at syndrome and symptom level.

Feldman et al. [19] reported a prevalence of 46% of psychiatric diagnoses in asthma patients and the estimation of psychopathology in severe asthmatics ranges between 30 and 63% [20,21]. Asthmatic patients with psychopathology achieve fewer goals related to asthma control, have more asthma associated ER visits and use more medication, all independent of the severity of asthma and demographics. Moreover, these patients tend to report higher levels of asthma symptoms than expected by their pulmonary function [19].

Psychopathology can be both causal and secondary to DA. Psychopathology may predispose asthma patients directly to an exacerbation through psychophysiological processes or it may predispose asthma patients indirectly through factors like non-adherence, and maladaptive coping styles [6,22,23] or misinterpretation of symptoms resulting in improper asthma management leading to poor asthma control [19,21–25]. Vice versa asthma, especially with frequent exacerbations as in DA, may increase the risk of developing psychopathology.

In light of the management strategies prescribed [3,14,26], which involves treating psychopathology if diagnosed, there is a need to study the association between psychopathology and disease outcome [27]. However, to our knowledge, a review of evidence from the literature on the importance of the identification and treatment of psychopathology in DA, has not yet been undertaken. Therefore, the aim of the present study was to review the literature with regard to (1) the prevalence of all psychopathology in general DA and in subcategories of DA; (2) evidence of associations between specific syndrome and symptoms of psychopathology and poor disease outcome in DA.

METHODS

Search

A comprehensive literature search of the PsycINFO database, MEDLINE database and Cochrane Library of English language abstracts was conducted on literature published from 1990 till July 2014 on psychopathology in DA. The search was conducted by pairing ''difficult asthma'' with keywords: psychological, psychology, psychiatric comorbidity, psychiatry, alexithymia, anxiety, panic, depression, affective, personality and psychopathology. Another search was conducted including subgroups of patients with DA by separately pairing ''refractory asthma'', ''near fatal asthma'', ''brittle asthma'', ''nocturnal asthma'', ''corticosteroid- resistant asthma'', ''corticosteroid-dependent asthma'', and ''therapy-resistant asthma'' with the same keywords as mentioned above.

Selection criteria

Psychopathology can be described both at syndrome and symptom level. Psychopathological syndromes refer to a specific set of symptoms and can be diagnosed with a semi-structured interview by trained professionals. Psychopathology at symptom level can be determined by self-report questionnaires. Studies meeting the following criteria were included in this review: (a) participants were patients with DA as defined by the ERS task force [26], or were patients with asthma in the following subgroups; refractory asthma, near fatal asthma, brittle asthma, nocturnal asthma, corticosteroid-resistant asthma, corticosteroid-dependent asthma and therapy-resistant asthma, (b) participants were adults above 18 years, (c) psychopathology was studied at symptom level or syndrome level, measured with standardized instruments, (d) statistical analyses were well described and (e) studies were published in English.

Once an initial pool of articles was obtained, titles were screened on inclusion criteria. Abstracts from retained records were assessed to identify potentially relevant articles and duplicates were removed. For the remaining records full texts were obtained and articles were added to the search by cross-reference of full texts (Figure 1). All eligible papers were submitted to close reading and were coded by two readers (L. P. and A. P.) on the following characteristics: (a) number of participants, (b) asthma diagnosis of participants, (c) instruments used to measure psychopathology, (d) statistical analysis, (e) design of the study and (f) main findings concerning psychopathology in DA. The results of the search are summarized in Tables 1, 2 and 3, describing results separately for DA in general and for each subgroup of DA.

RESULTS

The search initially identified 267 hits, of which 54 were potentially relevant, as is shown in Figure 1. After applying the above mentioned inclusion criteria, removing duplicates and adding 3 articles by cross referencing, the search resulted in 16 articles.

The studies are described in the tables; first specifically for DA (Table 1), second for the subgroups NFA and brittle asthma (Tables 2 and 3, respectively) to give a nuanced picture of the studies on psychopathology in DA.

Prevalence of all psychopathology in general DA

Four studies measured psychopathology at syndrome level (Tables 1, 2 and 3). Heaney et al. [30,31] reported 48% psychopathology in DA, Garden et al. [42] 40% and Rocco et al. [37] reported 11.7%. At symptom level Robinson et al. [32] reported 46%, Campbell et al. [35] 43%, Garden et al. [42] 40%, Ten Brinke et al. [29] 20.4% and Van Veen et al. [33] 20.11% psychopathology in DA. Only Miles et al. [43] and Garden et al. [42] studied psychopathology in patients with DA in comparison to patients with stable asthma. Miles et al. [43] found higher prevalence rates of psychopathology while
Garden et al. [42] found no differences.

Prevalence of all psychopathology in subcategories of DA

Anxiety and depression symptoms were studied in NFA-type of DA (Table 2). The reported prevalence rates ranged between 16.7% for state anxiety and 40.5% for depression [38]. Vázquez et al. [41] found no difference of prevalence of alexithymia (a personality trait which in a literal sense means ''without words for emotions'' [44]) between patients with NFA-type of DA and normal asthma while Plaza et al. [36] and Serrano et al. [40] reported more alexithymia in patients with NFA.

Associations between psychopathology syndrome and symptoms and poor disease outcome in DA

There were no studies on the relationship between disease outcome and psychopathology at syndrome level. At symptom level Heaney et al. [31] reported no relationship between psychopathology at symptom level and outcome in DA. Ten Brinke et al. [28] did report significantly more GP visits, ER visits, exacerbations and hospitalizations in patients with DA who displayed more psychopathology at symptom level. Campbell et al. [34] studied psychopathology in DA compared to patients who died of asthma and found no differences between groups for psychopathology. And vice versa, DA patients with worse outcomes, i.e. more exacerbations, reported significantly more psychopathology [29]. Alexithymia was associated with more hospitalizations [36] and more exacerbations [40] in patients with DA. Sández et al. [39] reported an association of reduced health-related quality of life and depressive symptoms.

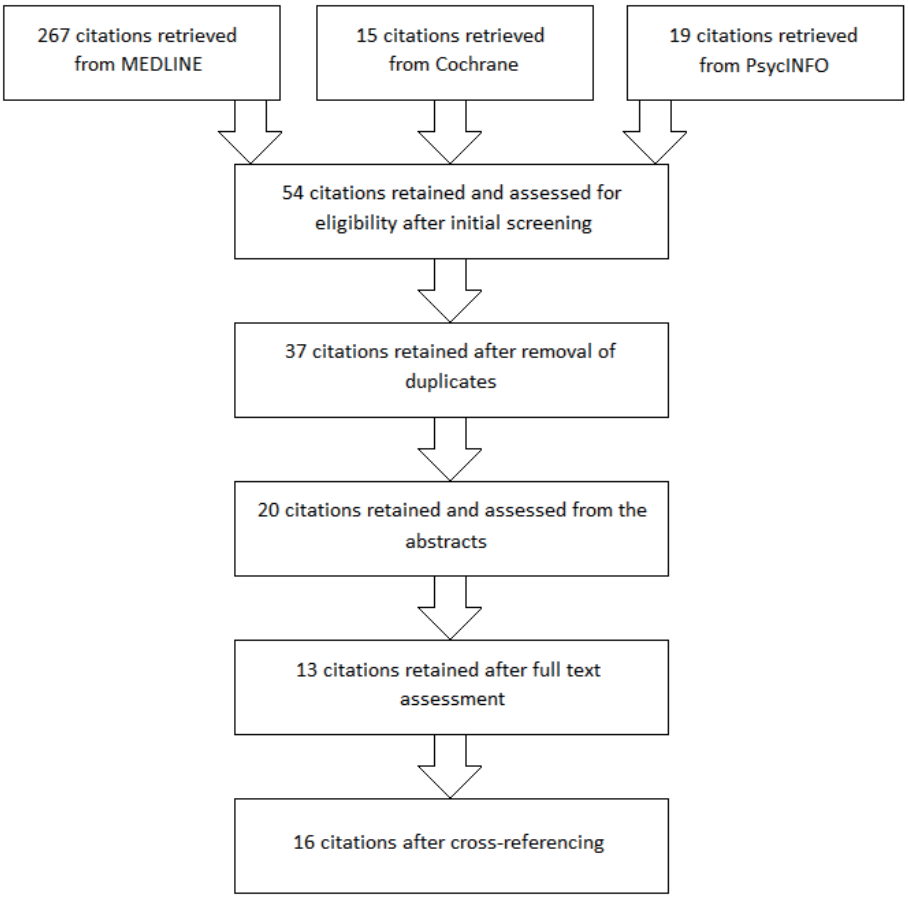

Figure 1. Flow diagram of the literature search.

Table 1. Psychopathology in DA

Study (first author)	Participants	Instrument	Statistical Analysis	Main Findings
Ten Brinke 2001 [28]	98 DA; 21 psychiatric caseness, 77 non caseseness	GHQ-12, Health care utilization questionnaire	Unpaired Student's t-tests, chi^2 analyses, nonparametric tests	Patients with psychiatric caseness have more: GP visits p=0.02, ER visits p=0.01, exacerbations p=0.02, hospitalizations p=0.04
Ten Brinke 2005 [29]	136 DA; 39 >3 exacerbations, 24 one exacerbation	GHQ-12	Unpaired t-tests, chi^2 analyses, logistic regression, nonparametric tests	20.4% psychiatric caseness in total of 136 patients, 18.4% in 63 patients. Patients with frequent exacerbations had higher score on psychological dysfunctioning p<0.05
Heaney 2003 [30]	34 DA, 39 NDA	HADS, psychiatric interview	Unpaired t-tests, chi^2 analyses, logistic regression,	48% psychiatric disorder, 45% unrecognized. No difference for psychiatric disorder, anxiety and depression scores
Heaney 2005 [31]	33 DA, 32 NDA	HADS, Systematic psychiatric interview, Juniper scale, AQLQ	Unpaired t-tests, chi^2 analyses	49% ICD10 psychiatric diagnoses, 48% in DA, 50% in non DA (ns). Anxiety and depression scores are higher in patients with ICD10 diagnosis (p<0.01). No relation ICD10 diagnosis and outcome of asthma. Better outcome for QoL in NDA p<0.001, More depression in DA p<0.05
Robinson 2003 [32]	56 DA	GHQ-30, psychiatric interview	Descriptive statistics	10 patients had a major psychiatric contribution to asthma (17.9%), psychiatric caseness in 26 patients (46%)
Van Veen 2008 [33]	136 DA; 29 obese, 107 nonobese	GHQ-12	Logistic regression analyses	20.11 % psychiatric caseness. 32% psychiatric caseness in obese patients, 16,9% psychiatric caseness in nonobese patients (p=0.10)

AQLQ= asthma quality of life score; DA = difficult asthma; ER = Emergency Room; GHQ = General Health Questionnaire; GP = General Practitioner; HADS = Hospital Anxiety and Depression Scale; ICD10 = International Classification of Diseases 10; NDA = non difficult asthma; ns= non significan; PC = poorly compliant; QoL = Qualtiy of Life

Table 2. Psychopathology in NFA

Study (first author)	Participants	Instrument	Statistical Analysis	Main Findings
Campbell 1994 [34]	154 NFA, 80 died of asthma	GHQ-28, IBQ, interview questionnaire	Mann-whitney, chi2, fishers-exact	No difference in psychiatric caseness and denial.
Campbell 1995 [35]	77 NFA	GHQ-28, Asthma Attitudes and Beliefs Questionnaire, IBQ	Spearman's correlation coefficient	43% psychiatric caseness, 57% denial. Positive correlation GHQ with morbidity ($p<0.05$) and stigmatization ($p=0.02$). No association GHQ and severity of asthma.
Plaza 2006 [36]	50 NFA, 25 asthmatic controls, 25 non-asthmatic controls	TAS, Borg scale,	Chi^2 analyses, oneway anova, kruskal wallis, man whitney, spearman's correlation coefficient	24% alexithymia in NFA. More alexithymia in NFA ($p<0.001$). Higher mean TAS score in NFA ($p=0.007$). Alexithymia is associated with more hospitalizations in NFA and non NFA ($p=0.036$). No difference for dyspnea.
Rocco 1998 [37]	17 NFA, 17 asthmatic controls	MMPI, HDA, Zung AD, psychiatric interview	t-tests	11.7% minor psychiatric episodes, no significant differences
Romero 2005 [38]	42 NFA	STAI, BDI, p-f scale of ASC	Spearman's rho coefficients, logistic regression analyses	21.4% p-f, 40.5 % depression ,2.4% severe depression (of 42 persons).16.7% state anxiety, 38.1% trait anxiety. State anxiety is a risk factor for the prescription of oral steroids ($p=0.015$). Panic-fear and trait anxiety were no risk factors.
Sández 2005 [39]	40 NFA	SF-36, BDI, p-f scale of ASC	Multiple regression	Depressive symptoms and p-f are associated with worse HRQL ($p<.01$)
Serrano 2006 [40]	179 NFA (64 alexithymic, 115 non-alexithymic), 40 asthmatic controls	TAS, GHQ-28	t-tests, mann whitney, chi^2 analyses, fishers' exact test logistic regression	36% alexithymia in NFA. More alexithymia ($p=0.004$) in NFA. Patients with NFA and alexithymia have more psychiatric caseness ($p=0.002$). Alexithymia is related to recurrent exacerbations ($p=0.049$)

Table 2. Psychopathology in NFA

Study (first author)	Participants	Instrument	Statistical Analysis	Main Findings
Vázquez 2010 [41]	44 NFA, 44 asthmatic controls	TAS, CDI, STAI-T, HSPK, BSSMA	Chi^2 analyses, student's t-test, multivariate analyses	36.4% trait anxiety. Higher levels of trait anxiety (p=0.001), depression (p=0.021). 9% was alexithymic. There was no difference for TAS overall score, there were more problems in describing feelings in NFA (p=0.002). No differences for self management and adherence.

BDI = Beck Depression Inventory; BSSMA = Brooks self-report Scales of Medication Adherence; CDI = Cognitive Depression Index; GHQ = General Health Questionnaire; HDA= Hamilton depression and anxiety scales; HRQL= Health Related Quality of Life; HSPK = Hypothetical Scenarios of Practical Knowledge; IBQ = Illness Behaviour Questionnaire; MMPI = Minnesota Multiphasic Personality Inventory; NFA = Near Fatal Asthma; p-f= panic and fear; p-f scale of ASC = panic fear scale of the Asthma Symptom Checklist; SF-36 = Short Form Health Survey; STAI = State Trait Anxiety Index; STAI-T = State Trait Anxiety Index, Trait; TAS = Toronto Alexithymia Scale; Zung AD = Zung Anxiety and depression scales

Table 3. Psychopathology in brittle asthma

Study (first author)	Participants	Instrument	Statistical Analysis	Main Findings
Garden 1993 [42]	20 BA, 20 asthmatic controls	GHQ-60, EPI, SCID, Life events interview	Binomial test, Shapiro Wilk test, paired t-test	40% psychiatric caseness and 40% current disorders; 3 mood disorders, 1 substance disorder, 6 anxiety disorders and 1 adjustment disorder. More current and past psychiatric disorders in brittle asthma (p=0.02). No difference in personality profiles or GHQ scores
Miles 1997 [43]	29 BA, 29 asthmatic controls	GHQ, LAQ, ASC, Clinical Interview	Chi^2 analyses	More psychiatric caseness in brittle asthma (p=0.0002). More problems in living with asthma in brittle asthma (p=0.002). In brittle asthma 55.2 % of patients delayed seeking help, 20.7% in non brittle asthma

ASC = Asthma Symptom Checklist; BA = Brittle asthma; EPI = Eysenck Personality Inventory ; GHQ = General Health Questionnaire; LAQ = Living with Asthma Questionnaire; SCID = Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders

DISCUSSION

Given the burden of DA and the role psychopathology plays in the treatment protocols of DA [2], it is remarkable that there are just few empirical literature studies on the association between psychopathology and DA. No studies were found on psychopathology in refractory asthma, nocturnal asthma, corticosteroid-resistant asthma, corticosteroid dependent asthma and therapy-resistant asthma.

Results on the prevalence of psychopathology on both symptom and syndrome level in DA were mixed but there is some evidence to indicate a higher prevalence of psychopathology in DA. The mixed findings are predominantly to be explained by the use of different instruments to assess psychopathology at different levels (symptoms versus syndrome). Another explanation could be the underestimation of symptoms in DA patients, possibly due to a high prevalence of alexithymia. Patients with alexithymia have difficulty discriminating between emotions and physical symptoms, which will limit the ability to recognize psychopathology and can possibly result in insufficient asthma management.

There were no studies at syndrome level on the association between psychopathology and exacerbations, but four studies [28,29,36,40] showed a relationship between psychopathology and exacerbations in DA at symptom level. Patients with DA as well as psychopathology experienced more asthma hospitalizations and exacerbations in comparison to patients with DA and less psychopathology [28]. And vice versa, patients with more exacerbations reported more psychopathology compared to patients with fewer exacerbations [29]. Although the direction of this relationship is still speculative, it supports not only the importance of diagnosing psychopathology in DA, but also the extension of the medical examination after an exacerbation with a psychiatric evaluation. We can only speculate whether the treatment of psychopathology also positively influences outcome in DA.

Limitations

Although in the last two decades, substantial efforts have been made in appropriately defining asthma [2,3] and specifically DA, the concept of DA is still not well described which makes it a very heterogeneous group of patients to study. Because of the small number of studies as well as the heterogeneity between studies, the use of different instruments, small sample sizes, it is also difficult to make cross study comparisons. Also, it is a question whether it is acceptable to compare DA to NFA and brittle asthma since they are subcategories of DA.

In summary, there is a higher prevalence rate of psychopathology in DA compared to the general population. Studies showing higher prevalence in DA compared to patients with stable asthma are equivocal. Alexithymia seems to be more common in DA compared to stable asthma and the general population but this association needs further consideration since all studies were performed in one country and only included patients/participants with a subcategory of DA (NFA). These findings should be replicated in other ethnic groups with DA.

Clinical relevance and future recommendations

There is some preliminary evidence that psychiatric evaluation should be included in medical examinations for individuals with DA who present with an exacerbation. Subsequently, psychological interventions could become a more prominent part of the rehabilitation program. The treatment of psychopathology could have an influence on outcome in DA, but further study is needed to increase insight into the relevance of treating psychopathology in DA.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Chapter 3

High level of psychiatric symptoms in patients with severe difficult asthma, an empirical study

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ABSTRACT

Objective: Evidence on the prevalence of psychiatric symptoms in difficult asthma (DA) is scarce and contradictory. Psychiatric symptoms are seen important in the treatment of DA, however the relation with perceived wellbeing is also scarce and contradictory. The aim was to assess the level of psychiatric symptoms in DA and its relation to perceived wellbeing.

Methods: 102 patients with DA, submitted for inpatient rehabilitation, were assessed during multidisciplinary assessment in a specialized asthma care center. The level of psychiatric symptoms was assessed with the SCL-90, perceived wellbeing with the SGRQ.

Results: Patients with DA reported significantly higher levels of psychiatric symptoms in comparison to the general population, approaching those of the psychiatric population. Significant and clinically relevant associations were found between psychiatric symptoms and perceived wellbeing and BMI, and between perceived wellbeing and BMI and exercise performance. Poor perceived wellbeing was most strongly associated with a higher level of psychiatric symptoms and in lesser extent to higher BMI and worse exercise performance. Psychiatric symptoms predicted worse perceived wellbeing.

Conclusions: This study reveals a high level of psychiatric symptoms and therefore stresses the importance of detecting psychiatric symptoms in patients with DA. Early referral to medical psychologists or psychiatrists is recommended.

INTRODUCTION

About 1.25 million people in the US have difficult asthma (DA) and are not responsive to maximal treatment according to international guidelines [1, 2]. These patients who have difficulty controlling their asthma symptoms are a treatment challenge and a significant clinical and financial burden for the health care system [3]. Patients with DA have increased risk of future exacerbations, hospital admissions and emergency room (ER) visits which have a negative impact on patients' perceived wellbeing [4-7]; for some patients DA can even lead to death. International guidelines on the treatment of asthma advocate a stepwise protocol (Global Initiative for Asthma, GINA[1]) [1], which mainly consists of five steps of pharmacological treatment, with the last step including systemic corticosteroids (apart from general recommendations e.g. avoiding asthma triggers, adequate drug compliance etc.). The treatment of patients with DA follows the last two steps as described in the GINA guidelines. Nevertheless, these patients still experience invalidating symptoms that significantly influence their daily life.

DA is considered to be related to psychiatric symptoms [1,2]. Psychiatric symptoms are known to have a negative impact in patients with asthma on adequate medication use, exacerbations and patients' perceived wellbeing and vice versa asthma symptoms negatively influence psychiatric symptoms [8-11]. Cause and consequence of psychiatric symptoms in asthma, and specifically DA, is unknown but is probably bi-directional [12]. Although psychiatric symptoms are associated with DA and are considered important in the treatment guidelines of DA [1, 6], research on the prevalence of psychiatric symptoms, especially the level of psychiatric symptoms, in DA is limited. Literature on psychiatric symptoms in DA and specifically the relation between psychiatric symptoms and patients' perceived wellbeing is both scarce and contradictory [13-14]. Two preliminary studies show a prevalence of psychiatric cases of respectively 21% [13] and 18% [14] in DA, which is comparable to the normal population. Robinson *et al* [15] however reported a higher prevalence of 46%. The former studies used cut-off scores to discriminate possible psychiatric cases and did not report the level of psychiatric symptoms. In addition, these studies did not compare the level of psychopathology to a norm group of the general and psychiatric population, which could give a more nuanced image of the severity of psychopathology.

1 GINA guidelines refer to an evidence based strategy of asthma management and prevention and consist of 5 steps. Patients receive step-wise treatment until they reach an acceptable level of control of asthma symptoms.

Therefore the present study aims first at assessing the level of psychiatric symptoms in a cohort of patients with DA and comparing this level with norm scores of the general and psychiatric population. Second, we study the relation between psychiatric symptoms and patients' perceived wellbeing, after correcting for confounders (i.e. obesity, age, female sex and physiological impairment) that are well known to negatively influence patients' perceived wellbeing.

METHODS

Setting

This cross-sectional study is conducted in 'Revant Centre for Pulmonary Rehabilitation', Breda, The Netherlands; a specialised tertiary asthma care centre that offers both inpatient and outpatient pulmonary rehabilitation. Asthmatic patients referred to inpatient rehabilitation have highly impaired health-related quality of life and no satisfactory response to prior medical and non-medical treatment by asthma specialists, often including outpatient rehabilitation [16,17]. These patients receive a comprehensive 3-months rehabilitation program on an inpatient basis by an interdisciplinary team of healthcare professionals, including pulmonologists and specialised health care psychologists, as recently described in detail elsewhere [16,17]. Patients enter the inpatient rehabilitation only after a multidisciplinary assessment of four days. Patients have to be abstinent from smoking if they want to participate in the rehabilitation program. All patients met GINA criteria for DA and received pharmacological treatment at step 4 or 5 of GINA criteria[1].

Participants and procedure

From November 2007 until June 2012, 193 asthma patients were referred for rehabilitation by pulmonologists from hospitals (flow diagram 1) for inpatient rehabilitation. After an initial screening by a pulmonologist and a pulmonary nurse on contra-indications as explained elsewhere [16] 126 patients entered a multidisciplinary assessment, including assessment by a psychologist, of four days to decide whether or not they were eligible for participation in the comprehensive treatment program. Eligibility was determined by 'the impact of asthma' on different dimensions of health status: physiological functioning, symptoms, activities, quality of life, health-care utilization during the previous year, motivation, commitment and feasibility [16]. Exclusion criteria for participation in the program were disorders and diseases both physical and

psychiatric that prevented a patient to participate in the treatment program. One patient was excluded because this patient did not use asthma medication. After assessment, 23 patients were excluded and did not enter rehabilitation resulting in a sample of 102 DA patients who entered the rehabilitation programme and whose data were analysed. Patient characteristics are shown in Table 1.

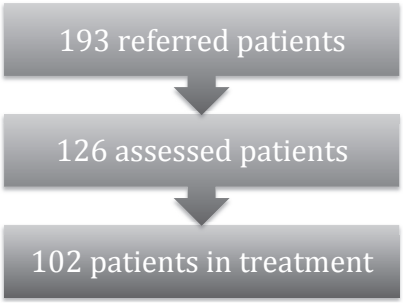

Figure 1. Flow diagram

MEASUREMENTS

During the standard multidisciplinary assessment, a comprehensive set of parameters was collected, which was part of usual assessment [16]. Only the tests within de scope of this paper are described below.

Psychiatric symptoms were measured with the Symptom Checklist (SCL90), a 90-item multi-dimensional self-report symptom inventory that measures different types of psychiatric symptoms [18]. All items are rated on a five point Likert scale ranging from 'not at all' to 'extremely' to indicate the extent to which a symptom has bothered or distressed someone in the past four weeks, the higher the score the higher the level of psychiatric symptoms. The checklist has an overall score (general psychiatric symptoms) and sub-scores on eight dimensions. The SCL90 has been used worldwide and validated in The Netherlands in men and women, the general population and in psychiatric samples, resulting in norm-scores indicating 'very low' to 'very high' scores [18]. Total scores are used for the level of psychiatric symptoms. It should be remembered that scores in The Netherlands are not recoded to zero and scores range from 90 to 450.

Patients' perceived wellbeing was measured with the Saint George Respiratory Questionnaire (SGRQ), a 76 item questionnaire with three sub-domains, i.g. symptoms, activity and impact [19]. A summary score is calculated by empirically weighted item scores. Scores range from 0 (no impairment) to 100 (maximal

impairment). The summary score is used in this study. The SGRQ has proven to be a valid and reliable instrument [19].
Physiological impairment was measured by airway obstruction and exercise performance. Lung function was measured by the ratio between the amount of air, which can be forcibly exhaled from the lungs in the first second of a forced exhalation (FEV1, Forced Expiratory Volume in One Second). Exercise performance was measured by the maximal power output on a cycle ergometer (W-max) that has both good reliability and validity [20]. W-max measures the highest workload a patient can reach, and for how many seconds this can be maintained. People who are in good shape generally have higher W-max values (normalized for sex, age and height) and can therefore exercise more intensely than those with worse condition. In addition, demographics and BMI were assessed.

Ethical Principles

This study was review board exempt since all assessments are part of usual care provided by the rehabilitation centre and all data were anonymized. Patient's informed consent was obtained for the utilization of the data for research purposes.

Statistical Methods

All statistical analyses were performed with the IBM SPSS Statistics for Windows Version 22.0 [21].
To determine the level and severity of psychiatric symptoms in participants, descriptive statistics were used to calculate means and standard deviations of the scores on the SCL90 and its subscales. Analyses were conducted separately for men and women, and displayed together with the average scores of the general population and a psychiatric sample for comparison. Differences between the average total scores of the population with DA, the general population and the psychiatric sample were analysed using one sample t-tests by taking the lowest mean score as hypothetical value. Differences between men and women for the SCL90 total score and its subscales were analysed using independent samples t-tests.
In addition, the correlations between SCL90 total score, FEV1%, W-max, BMI and SGRQ were determined by Pearson correlation coefficients; *p*-values were considered statistical significant when $p < 0.05$. However, since statistical significance provides little information when calculating correlation coefficients,

clinical relevance was determined using Cohen's criterion [22]. According to this criterion correlations of $r \geq 0.10$ correspond with small, $r > 0.30$ with medium and $r > 0.50$ with large effect-sizes, the latter two are considered clinically relevant [22]. Multivariate linear regression analyses were performed with the SGRQ as dependent variable and the SCL-90 as independent variable. Several confounders (age, gender, BMI, W-max, FEV1%) were entered as separate blocks. The R-square statistic was determined to indicate the proportion of explained variance, and the F-change statistic was determined to indicate the significance of adding separate blocks. In addition, a path analysis via regression analysis was performed using first, a regression analysis with the SCL-90 as dependent variable and BMI and W-max as predictors. Second a regression analysis was performed with SGRQ as dependent variable and BMI, W-max and SCL-90 as predictors. The amount of variance that cannot be accounted for by the endogenous variables, including measurement error, are depicted in the unexplained variance, i.e. 'e' or error terms in the model.

RESULTS

In the total sample of patients with DA, patients were more likely to be female (72%, 73/102) (table 1). Means and standard deviations (SD) of the scores on the subscales of the SCL-90 for men and women are shown in table 2. The scores are presented separately for males and females, together with the mean scores and SD's of the general population and a psychiatric sample. Differences between subscales and total scores between males and females were calculated. There were no significant differences between males and females for both scores on the subscales and the total score of the SCL-90 and for SGRQ total scores.
Differences between total scores for females and males for patients with DA, the general population and the psychiatric population were calculated. Female patients with DA reported significantly higher SCL-90 total scores compared to the general population $t(72) = 7,3$, $p<0.001$ and significantly lower total scores compared to the psychiatric population $t(72) = 7,5$, $p<0.001$. Male patients with DA also scored significantly higher in comparison to the general population $t(28) = 5,7$, $p<0.001$ and significantly lower in comparison with the psychiatric population $t(28) = 2,8$ $p<0.001$.
Subsequently, Pearson's correlation coefficients were calculated to analyse the correlations between the SGRQ and SCL-90 total score, FEV1%, W-max% and BMI. All correlations are displayed in table 3. Correlations between SCL-90 and SGRQ and SCL-90 and BMI were both statistically significant and clinically

relevant with small to medium effect sizes (r=0.47, r=0.23 respectively). In addition, the correlations between SGRQ and W-max% and SGRQ and BMI were both statistically significant (p<0.01) and clinically relevant with medium effect sizes (r=0.34, r=-0.36 respectively). The correlation between W-max% and FEV1% was also statistically significant (p<0.01) and clinically relevant with a medium effect size (r=0.38). As can be seen in table 3, SCL-90 scores were not significantly correlated with W-max% and FEV1%. A multiple linear regression (dependent variable: SGRQ, independent variable SCL-90) revealed that all variables except for age and gender had a significant association with SGRQ, together explaining 33% of all variance (table 4).

Table 1. Characteristics of patients with difficult asthma (N=102)

Characteristics	N	%	Mean	SD	Range
Demographics					
Female	73	72			
Age			47	15	18-79
BMI			30	6	18-50
<18,5	1	1			
18,5-25	22	22			
25-30	32	31			
>30	47	46			
Smoking history	45	44			
Use of oral corticosteroids	24	24			
Physiological measures					
FEV1 % p			87	22	24-131
W-max %			71	23	14-128
Psychological measures					
SCL-90*			171	56	92-372
SGRQ			62	17	20-92

Abreviations: BMI, Body Mass Index; FEV1%, forced expiratory volume in 1 second predicted; W-max%, maximal power output on cycle ergometer predicted; SCL-90, Symptom Checklist; SGRQ, Saint George Respiratory Questionnaire
*It should be remembered that scores in The Netherlands are not recoded to zero and scores range from 90 to 450.

Specifically, BMI, W-max% and SCL-90 were significantly and independently associated with the SGRQ. Respectively, BMI explained 11%, FEV1% 8% and SCL-90 12% of total variance. The path model shows small effects of predictors on the SGRQ except for the SCL-90, which has a medium effect of 37% (figure

2). The direct effects of W-max% and BMI are about equal to their indirect effects. Both the SCL-90 (e=0,96) and the SGRQ (e=0,82) are explained mostly by outside variables.

Table 2. Mean SCL90* scores of 102 patients with difficult asthma receiving rehabilitation with mean SCL90 scores of the general population and psychiatric sample

	Men (N= 29)			Women (N=73)		
	Rehabilitation (SD)	**General Population (SD)**	**Psychiatric Population (SD)**	**Rehabilitation (SD)**	**General Population (SD)**	**Psychiatric Population (SD)**
ANX	18,6 (7,6)	11 (4.3)	23-27 (9.5)	17,9 (8,5)	13 (5.7)	27-30 (10.2)
PH-ANX	10,4 (4,6)	7 (2.1)	11-13 (6.7)	11,6 (7,7)	7 (3.5)	12-15 (7.7)
DEP	32,3 (11,7)	18-20 (6.3)	37-43 (14.4)	31,4 (10,8)	21-22 (8.6)	44-50 (15.2)
SOM	28,1 (10,4)	15 (5.7)	24-27 (9.6)	28,0 (10,0)	16-18 (7.1)	26-30 (10.2)
IN	21,1 (7,4)	12 (4.6)	20-23 (7.9)	21,9 (6,9)	13-14 (5.1)	21-24 (8.5)
SEN	30,6 (13,4)	23-24 (6.8)	35-40 (14.7)	28,5 (10,1)	23-26 (8.8)	38-45 (16.0)
HOS	8,9 (3,2)	6 (2.5)	10 (5.1)	10,0 (4,1)	6 (2.4)	10-11 (5.5)
SLEEP	8,0 (3,9)	3 (2.4)	5-6 (3.6)	7,2 (3,7)	4 (2.8)	7-8 (3.8)
Total PSY	171,5 (56,4)	108-115 (27.3)	187-210 (62.1)	169,4 (56,0)	117-129 (36.4)	208-234 (67.6)

ANX, anxiety; PH-ANX, phobic anxiety; DEP, depression; SOM, somatization; IN, inadequacy of thought and action; SEN, interpersonal sensitivity and paranoid ideation; HOS, hostiligy; SLEEP, sleeping problems; Total PSY, general psychopathology.
*. It should be remembered that scores in The Netherlands are not recoded to zero and scores range from 90 to 450.

Table 3. Correlations between psychiatric symptoms, health status and physiological impairment (N=102)

	BMI	**FEV1%**	**Wmax%**	**SCL-90**
BMI	.	.	.	.
FEV1 %	-0,04	.	.	.
Wmax %	-0,17	0,38**	.	.
SCL-90	0,23*	0,07	-0,19	.
SGRQ	0,34**	-0,09	-0,36**	0,47**

* Correlation is significant at $p < 0.05$ level
** Correlation is significant at $p < 0.01$ level
Abbreviation: BMI= Body Mass Index, FEV1=Forced Expiratory Volume in one second, pred = predicted, Wmax= maximal output on cycle ergometer,
SCL-90= Symptom Check List, SGRQ= St. George's Respyratory Questionnaire

Table 4. Multiple linear regression analysis with patients' perceived wellbeing (SGRQ) as the dependent variable

	95% CI				
	Beta	**Low**	**Upper**	***p***	
I					
Age	0,11	-3,87	14,00	0,26	
Gender	0,06	-197,71	383,07	0,53	
II					
BMI	0,33	15,13	55,83	0,00*	
III					
FEV1 % pred	0,05	-4,39	7,25	0,63	
W-max % pred	-0,32	-15,04	-3,30	0,00*	
IV					
SCL-90	0,37	2,35	6,51	0,00*	
Model I					
R square					0,02
F Change					0,91
Sig. F Change					0,41
Model II					
R square					0,13
F Change					11,97
Sig. F Change					0,00*
Model III					
R square					0,21
F Change					5,02
Sig. F Change					0,00*
Model IV					
R square					0,33
F Change					17,90
Sig. F Change					0,00*

* Independent variable is significant at the 0.01 level (2-tailed)
Abreviations: BMI, Body Mass Index; FEV1, forced expiratory volume in 1 second; W-max, maximal power output on cycle ergometer; % pred, % predicted; SCL-90, Symptom Checklist; SGRQ, Saint George Respiratory Questionnaire

DISCUSSION

This study demonstrates that patients with DA report high levels of psychiatric symptoms. The level of psychiatric symptoms is significantly higher compared to the general population and approaches those of the psychiatric population. By comparing the level of psychiatric symptoms with the general and psychiatric population, this study provides an impression of the severity of psychiatric symptoms in these patients with severe DA.

In our study, males and females reported no differences in psychiatric symptoms as well as perceived wellbeing. This is striking because in general, females tend to report higher levels of psychiatric symptoms in comparison to men [23]. And one would expect to find a similar trend in the present sample especially since females with asthma tend to report more asthma symptoms and worse perceived wellbeing compared to male patients, despite having similar or better lung function [24]. Therefore in patients with DA, we should consider high levels of psychiatric symptoms, despite of gender.

These patients with severe DA and high levels of psychiatric symptoms tend to report lower perceived wellbeing and tend to have higher BMI's while age, gender, physical impairment and airway obstruction were not related to psychiatric symptoms or perceived wellbeing. This may be explained by the fact that the electively measured lung function does not capture the variability of the lung function, which is characteristic of asthma.

Psychiatric symptoms were significantly and independently related to perceived wellbeing. Our path model supported this relation. In particular, the level of psychiatric symptoms most strongly predicted perceived wellbeing in comparison to BMI and exercise performance. In this model, psychiatric symptoms hardly mediated the small effect of BMI and exercise performance on wellbeing. Considering these results, we could suggest that psychopathology has a larger influence on wellbeing in patients with DA than parameters like, age, gender, BMI, airway obstruction and exercise performance. Moreover, since perceived wellbeing is used to measure progress in rehabilitation [16], it appears especially important to specifically consider treating psychiatric symptoms in DA if one wants to improve wellbeing in DA.

Our study has several limitations. First, variables like personality, traumatic experiences, Socioeconomic Status (SES) or other physical parameters were not corrected for in our model that could mediate the relation between psychiatric symptoms and perceived wellbeing. Another limitation is the fact that these findings refer to severe DA patients and are not generalizable to the general population of asthma. Although we used a relatively large sample size, using a

sample from only one rehabilitation center further decreased generalizability. However, our population is similar to other populations with DA with regard to male/female ratio and SGRQ scores [15], which makes our study exemplar for patients with DA. Both severe somatic and psychiatric disorders that obviously needed treatment were excluded from rehabilitation. This further supports our findings of high levels of psychiatric symptoms in DA.

This study is a first start in the research on psychiatric symptoms in DA and does not allow for inferences about causality, i.e. whether psychiatric symptoms are a cause or consequence in DA. Therefore to obtain a clear understanding of this relation longitudinal research is recommended. In addition, research on the effect of treating psychiatric symptoms in DA on both the prevalence of psychiatric symptoms itself, on DA symptoms and the impact on perceived wellbeing is recommended. In addition, other possible mediating factors like personality, SES and other physical parameters should be considered in future studies.

In conclusion our findings reveal the importance of detecting psychiatric symptoms in patients with DA, independent of the severity of airway obstruction or of gender. Early referral to medical psychologists or psychiatrists is recommended. Our study gives an opportunity to improve the treatment of DA by further studying whether the treatment of these high levels of psychiatric symptoms indeed improve perceived wellbeing in patients with DA and thus lessen the burden of patients.

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Chapter 4

Unrecognised psychopathology in patients with difficult asthma: Major mental and personality disorders

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ABSTRACT

Background: Difficult asthma is a severe subgroup of asthma in which the main feature is uncontrollability of symptoms. Psychopathology is suggested to be prominent in patients with difficult asthma and considered important in its treatment; however, the evidence is scarce.

Aims: To describe psychopathology in difficult asthma, both major mental and personality disorders, based on diagnostic interviews.

Method: This study was conducted in a specialised asthma care centre. A total of 51 patients with difficult asthma were diagnosed at the start of the treatment programme using two structured clinical interviews for both major mental (SCID-I) and personality disorders (SCID-II) according to DSM-IV-TR.

Results: About 55% of the patients with difficult asthma had a psychiatric disorder of which 89% was undiagnosed and untreated before being interviewed. About 49% had a minimum of one major mental disorder of which the cluster of anxiety disorders was the most common cluster of major mental disorders, followed by somatoform disorders. About 20% were diagnosed with a personality disorder. Of the 10 patients with a personality disorder, 9 had an obsessive–compulsive personality disorder.

Conclusions: This study demonstrates that more than half of patients with difficult asthma had a psychiatric disorder of which 89% was unrecognised. This study highlights the importance of offering patients with difficult asthma a psychiatric diagnostic interview and/or a psychiatric consultation as part of their routine medical examination and provision of appropriate psychiatric treatment. Moreover, it highlights the urgency of further research into the role of psychopathology in the development of difficult asthma.

INTRODUCTION

Asthma is a lifelong respiratory disease characterised by airway obstruction, airway inflammation and bronchial hyperresponsiveness [1]. Asthma is a global health problem [1], which affects about 1 in 12 people in the USA (8% of 316 million, 25 million) and numbers are increasing every year [2]. International guidelines on the treatment of asthma advocate a stepwise approach (Global Initiative for Asthma, GINA) [1]. This stepwise approach consists mainly of five steps of pharmacological treatment, the final step including systemic corticosteroids (apart from general recommendations of avoiding asthma triggers, adequate drug compliance, etc.). In most asthmatic patients, the occurrence of symptoms and/or asthma attacks can be controlled with the GINA approach. However, there is a subcategory of asthmatic patients who cannot control their symptoms despite treatment at step 4 or 5 of the GINA guidelines [1]. In clinical practice, these patients are defined as those who present with difficult asthma [3] affecting approximately 5% of the asthmatic population [4]. This would mean that about 1.25 million people in the USA and 2.5 million in Europe suffer from difficult asthma [1].

Difficult asthma has a profound impact on health status and quality of life [5]. Patients with difficult asthma have frequent exacerbations that can result in hospitalisations, emergency room visits [6, 7] and days of absence from work or school [8]. Moreover, patients with difficult asthma have an increased risk of sudden asthma death and adverse effects of high-dose corticosteroids [6]. Although the interest in difficult asthma has grown considerably, the aetiology of difficult asthma is poorly understood. It is well known that major mental disorders are highly prevalent (31%) in asthma patients in general [9] compared with the general population (26%) [10]. This 31%, however, encompassed both patients with treatable asthma and difficult asthma, which leaves the question whether the higher prevalence could be attributed to patients with asthma in general or to the difficult asthma population specifically. The prevalence of major mental disorders in difficult asthma appears to be high, but is hardly studied [11]. Two studies by Heaney et al. [11, 12] showed a prevalence of 49% in difficult asthma. However, these studies did not use structured interviews and used ICD-10 criteria instead of the DSM-IV-TR13 criteria for assessing mental and personality disorders. These studies did report 81.3% of mental disorders to be unrecognized [11]. Although there is a recent publication on personality traits in difficult asthma [14], to the best of our knowledge the prevalence of personality disorders in difficult asthma has not been previously reported utilising systematic research diagnostic interviews.

Therefore, the current study assessed the prevalence of psychopathology in difficult asthma focusing on both major mental and personality disorders using research diagnostic interviews according to the DSM-IV-TR [13].

METHOD

Setting

This study was conducted in Asthma Centre Heideheuvel, Hilversum, The Netherlands, a specialised asthma care centre that offers in-patient pulmonary rehabilitation. Asthmatic patients referred to in-patient rehabilitation have highly impaired health status and no satisfactory response to prior medical and nonmedical treatment by asthma specialists, often including outpatient rehabilitation [15, 16]. These complex patients with difficult asthma receive a comprehensive 3-month rehabilitation programme on an in-patient basis by an interdisciplinary team of healthcare professionals, including pulmonary physicians and specialised healthcare psychologists, as described in detail elsewhere [15, 16]. Patients enter the rehabilitation centre only after a multidisciplinary assessment of four days, confirming their indication. Patients have to be abstinent from smoking during rehabilitation.

Participants

During a period of 17 months, 65 patients with difficult asthma entered the treatment programme and were invited to participate in the current study. This included, apart from the standard intake programme, a psychiatric interview. Seven patients did not give informed consent and another seven patients dropped out during the intake of the rehabilitation programme before diagnostic interviews were performed. The remaining 51 patients consented to participate. Their characteristics are shown in Table 1.

Measurements

In the first weeks after the start of the programme, each patient was interviewed by trained psychologists with the structured clinical interview (SCID-I) [17] diagnosing major mental disorders and the structured clinical interview (SCID-II) [18] diagnosing personality disorders, both according to DSM-IV-TR [13].

Table 1. Characteristics of patients with DA (N=51)

Characteristics	N	Means ± S.D.
Sex, M/F	10/41	
Age, years		43 ± 15
Education		
low	15	
middle	24	
high	12	
SES		
low	7	
middle	43	
high	1	
BMI		
<24,9	12	30 ± 7
25-29,9	16	
>30	23	
FEV1 %		88,5 ± 24,2
GINA		
Step 4	7	
Step 5	44	

SES = Socioeconomic Status; BMI = Body Mass Index; FEV1% = % predicted forced expiratory volume in 1 second; GINA = Global Initiative for Asthma

Ethical principles

Both the institutional medical ethics committee of the Asthma Centre and the medical ethics committee of the Utrecht Medical Centre approved the study protocol according to Dutch law. Patients were sent information about the study before they agreed on participation. All patients gave written informed consent.

Statistical methods

Statistical analysis was performed using SPSS Statistics for Windows Version 19.0. To determine characteristics and psychopathology of the participants, descriptive statistics were used. Associations between subgroups of patients were analysed using chi-square statistics.

RESULTS

The characteristics of the 51 patients with difficult asthma are shown in Table 1. Of these, 41 patients (80.4%) were female, 45.1% were obese, 47.1% had a medium educational level and 84.3% middle-class SES. Of the 51 patients with difficult asthma, 28 patients (54.9%) had one or more major mental and/or personality disorders (Table 2).

Table 2. Major mental and personality disorders in 28 out of a sample of 51 Difficult Asthma patients who were referred to our specialized asthma care center (DSM-IV-TR).

	Total (N=28) N (%)	**Females (N=41) N (%)**	**Males (N=10) N (%)**
Psychiatric disorders[2]	28 (54,9)	26 (63,4)	2 (20)
Major mental disorders	25 (49,0)	24 (58,5)	1 (10)
Mood disorders	12 (23,5)	12 (29,3)	1 (10)
Major depressive disorder	9 (17,6)	9 (22,0)	0
Dysthymic disorder	2 (3,9)	2 (4,9)	0
Bipolar disorder	1 (2,0)	1 (2,4)	0
Anxiety disorders	15 (29,4)	12 (29,3)	1 (10)
Social phobia	4 (7,8)	4 (9,8)	0
Specific phobia	5 (9,8)	4 (9,8)	1 (10)
PTSD	4 (7,8)	4 (9,8)	0
Panic disorder	1 (2,0)	1 (2,4)	0
OCD	1 (2,0)	1 (2,4)	0
Substance disorders	1 (2,0)	1 (2,4)	0
Substance abuse disorder	1 (2,0)	1 (2,4)	0
Somatoform disorders	12 (23,5)	11 (26,8)	1 (10)
Somatization disorder	5 (9,8)	5 (12,2)	0
Undifferentiated somatoform disorder	4 (7,8)	3 (7,3)	1 (10)
Pain disorder	3 (5,9)	3 (7,3)	0
Personality disorders	10 (19,6)	9 (22)	1 (10)
Borderline personality disorder	1 (2,0)	1 (2,4)	0
Avoidant personality disorder	3 (5,9)	3 (7,3)	0
Obsessive compulsive personality disorder	9 (17,6)	8 (19,5)	1 (10)
Dependent personality disorder	1 (2,0)	1 (2,4)	0
Personality disorder NOS	1 (2,0)	2 (4,9)	0

PTSD, Post traumatic stress disorder, OCD, obsessive compulsive disorder, NOS, not otherwise specified

Females were more likely to have a major mental disorder (58.5%) compared with male patients (10.0%; $\chi 2=7.58$, d.f.=1, P=0.006), which was not the case for personality disorders. As can be seen, 25 out of 51 patients (49.0%) had a major mental disorder, and 10 out of 51 patients (19.6%) had a personality disorder. Seven out of 51 patients (13.7%) reported both a major mental disorder and a personality disorder. Ten out of 51 patients (19.6%) reported more than one major mental disorder and 3 out of 51 patients (5.9%) reported more than one personality disorder. Overall, anxiety disorders (29.4%) were the most common cluster of disorders, followed by somatoform disorders (23.5%) and mood disorders (23.5%). Airway obstruction (FEV1%) did not differ between the patients with and without a psychiatric diagnosis (data not shown).

Of the 28 patients who were diagnosed with a psychiatric disorder, 3 patients had had a psychiatric diagnosis before referral to the rehabilitation centre: one had an obsessive–compulsive personality disorder (receiving psychotherapy), one had a somatization disorder (receiving psychotherapy) and one patient had a major depressive disorder (using antidepressants). This means that 25 of the 28 (89.3%) patients had a psychiatric diagnosis, which was not diagnosed before. Of the 23 patients who were not diagnosed with a psychiatric disorder according to the structured interviews, one patient received antidepressants and another six patients received benzodiazepines for sleeping problems (all prescribed by their GP).

DISCUSSION

This is one of the first studies in patients with difficult asthma assessing psychopathology using the DSM-IV-TR criteria [19, 20]. The strength of the current study is the involvement of structured interviews (SCID-I and SCID-II) in order to get a DSM-IV-TR classification. The current study showed that over half (54.9%) of the patients with difficult asthma referred to the specialized asthma care centre had one or more psychiatric disorders (89.3% of which were previously unrecognised). Specifically, 49% of all patients had a major mental disorder and 19.6% were diagnosed with a personality disorder. Heaney et al. [11, 12] reported a similar prevalence (49%) of major mental disorder in patients with difficult asthma of which 81.3% was unrecognised. However, this study did not use structured interviews and diagnosed according to ICD-10 criteria. This prevalence is higher in comparison to the 31–34% reported by two studies by Lavoie et al. [9, 21] in asthmatic out-patients, encompassing both 'normal' asthmatic patients and patients with difficult asthma. The prevalence of

49% of major mental disorder in the current study is also substantially higher in comparison to the prevalence in the general population in the USA (26.6%)10 and in The Netherlands (18%) [22]. Similarly, the prevalence of personality disorders of 19.6% in the current study is also substantially higher compared with the general population in the USA (9%) [23] and in The Netherlands (13.5%)[24].

In the current study, the cluster of anxiety disorders was most common (29.4%) followed by somatoform disorders (23.5%) and mood disorders (23.5%), respectively. Specifically, major depressive disorder was the most common major mental disorder (17.6%) diagnosed and obsessive–compulsive personality disorder (17.6%) was the most commonly diagnosed personality disorder.

The current study is among the first using research-based standardised instruments based on DSM-IV-TR criteria to assess a wide range of DSM disorders including personality disorders in difficult asthma. Since we studied a group of patients with complex asthma in one specialised asthma care centre, the question remains open whether these findings are generalizable to the total population of patients with difficult asthma. In the current study, all patients did have difficult asthma according to GINA guidelines. However, patients who smoked, patients without sufficient learning ability for the (intensive) rehabilitation programme (e.g. because of intellectual disability, neuropsychological problems, motivational problems) and patients with known psychiatric or medical diseases interfering with this programme were excluded (as part of general policy of the rehabilitation centre) which might have resulted in an underestimation of the prevalence of psychiatric disorders. And the small number of male participants does not warrant a conclusion about differences between male and female patients with difficult asthma.

About 89.3% of the patients with difficult asthma in the current study who received a psychiatric diagnosis were not diagnosed. Because of the dramatic manifestation of difficult asthma, psychiatric symptoms like anxiety or panic can be mistaken for asthma symptoms, which might explain the high number of unrecognised psychiatric disorders. Moreover, stigma about psychiatric disorders, for instance, resulting in being afraid that a psychiatric disorder would negatively impact asthma treatment, could cause unwillingness to acknowledge and accept psychiatric symptoms [25].

Although beyond the scope of the current study, an important question about the direction of the relation is: is psychopathology a contributor or a consequence of difficult asthma? Psychiatric symptoms could worsen asthma symptoms and the dramatic manifestation of asthma symptoms in difficult

asthma could probably cause or worsen psychiatric symptoms. However, the impact of psychiatric symptoms on difficult asthma does not appear to be a straightforward one [11]. Moreover, because by definition, most patients with difficult asthma use corticosteroids and it is well known that these drugs have major psychotropic side-effects, a possible independent effect of this medication on major mental disorders should be taken into account [26]. Psychological distress is heightened in patients with severe prednisone dependent [14] and the use of oral corticosteroids are related to lower quality of life [27]. Several psychiatric disorders are significantly associated with adult-onset asthma [28]. Prospective research is needed in which patients who develop difficult asthma after a prior diagnosis of asthma are followed and for patients with a first diagnosis of a psychiatric disorder and with a first diagnosis of asthma, to elucidate on a possible contributing role of psychiatric disorder in difficult asthma.

Both major mental disorders and personality disorders [29] have a substantial impact on quality of life, which is known to be poor in patients with difficult asthma [30]. Based on the effect of psychiatric therapy in general [31], it is reasonable to suggest that the treatment of major mental and personality disorders also improves quality of life in difficult asthma. In chronic obstructive pulmonary disease (COPD), a severe pulmonary disease in which also high doses of corticosteroids are used, comparable figures of psychiatric disorder are reported [32]. In this population, the risk of missing diagnoses and treatment of concurrent psychiatric disorder is also high [32]. Studies on the treatment of psychiatric disorder in COPD show improvement for both physical and psychiatric complaints [32]. Given these results, one might hypothesise that similar outcomes of treatment might be obtained in a difficult asthma population. Future research is needed to determine the benefit of psychotherapy and/or pharmacotherapy in standard difficult asthma treatment.

This study advocates the importance of offering patients with difficult asthma a psychiatric diagnostic interview and/or a psychiatric consultation as part of their general medical examination since 54.9% of patients with difficult asthma were diagnosed with a psychiatric disorder, most of them unrecognised and untreated. Furthermore, the results stress the urgency of further research into the potential roles of mental disorders in difficult asthma and of difficult asthma in mental disorders.

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Chapter 5

A systematic review on the relation between alexithymia and asthma

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ABSTRACT

Objective: Alexithymia is considered a complicating factor of asthma. Patients with alexithymia do not adequately perceive emotions and bodily sensations as is necessary in asthma in order to be able to control asthma symptoms. This can lead to non-optimal asthma management and low quality of life. We reviewed the available literature on empirical findings regarding the prevalence, relation with severity of asthma, asthma control, quality of life and treatment of alexithymia in asthma.

Methods: Studies in English language journals using MEDLINE were retrieved by an electronic search published from 1990 till July 2015.

Results: The search identified 11 empirical studies. The results showed that the prevalence of alexithymia in asthma was high and alexithymia was related to more severe levels of asthma symptoms, worse asthma control and lower quality of life. No studies regarding treatment of alexithymia in asthma were found.

Conclusions: The prevalence of alexithymia in asthma is high and it is related to the severity of asthma, worse asthma control and lower quality of life. Future research should focus on the role of alexithymia in asthma and specifically if treatment of alexithymia in asthma improves outcome.

INTRODUCTION

Asthma is a highly prevalent respiratory disease [1]. Its incidence is rising, becoming a growing health problem in society [1]. Asthma is in general a well treatable chronic disease. Treatment is first aimed at keeping the airways in the best possible state and is, secondly, aimed at gaining control over the disease, hence maximizing symptom free periods [2-3]. Optimal control over asthma results in minimal or absent impact of the disease on quality of life [4]. Severity of asthma is classified based on responsiveness to treatment [2,5] e.g. the level of control over asthma (severity based on GINA criteria [2]). Not all patients achieve optimal control over asthma symptoms, which can lead to frequent exacerbations and hospitalizations [6-8] and hence low quality of life. Difficult asthma (DA) is a severe kind of asthma in which patients cannot control the manifestation of the disease despite being maximally treated [7-8].

Alexithymia, as one of the patient related factors, is associated with insufficient disease control in asthma [9]. Literally alexithymia means without words for emotions [10]. It consists of four aspects: (1) difficulty identifying and describing feelings; (2) difficulty distinguishing feelings from bodily sensations; (3) reduction or absence of symbolic thinking; (4) utilitarian thinking without fantasy [11]. Alexithymia is a dimensional concept that can be present from low negligible levels to high pathological levels [12]. It is strongly related to concepts as psychological mindedness [13], emotional intelligence [14] and mentalization [15].

Alexithymia is considered a risk factor for both psychiatric and somatic diseases that are influenced by disordered affect regulation [16]. For asthma patients adequate perception of bodily sensations is essential to 1) describe asthma symptoms toward their doctors so they can treat them accordingly 2) seek help/ treatment if necessary 3) take medication when necessary [17]. Patients with asthma need to be able to adequately perceive bodily sensations [17]. However, patients with alexithymia specifically have an impaired ability to create mental representations of emotions, which is necessary to be able to distinguish between feelings and bodily sensations; as a consequence alexithymia can be regarded as an impairment that may lead to the misinterpretation / misperception of physical symptoms [4, 18-20]. At one hand, alexithymia tends to influence illness perception resulting in over reporting and catastrophizing of somatic sensations and symptoms resulting in poor illness behaviour [4,21]. On the other hand, underestimation of both physical and emotional sensations and interpretation of symptoms may result in non-optimal medication use, more exacerbations, hospitalisations and therefore worse control over asthma symptoms and low

quality of life [4,21]. Alexithymia can be seen as a complicating factor in the development and sustainment of uncontrolled (difficult) asthma or as a consequence of the overwhelming nature of severe asthma symptoms [21].
Empirical evidence of alexithymia as a patient related factor in asthma appears to be scarce [22]. Alexithymia research in asthma started in 1980 by Kleiger et al. 23-24] and was followed by several studies [25-27]. Asthma was considered a psychosomatic disease and alexithymia as associated with the development of asthma [28]. However, research showed little evidence indicating that alexithymia is associated with the development of asthma. The focus of research changed into alexithymia as a complicating factor in asthma, resulting into a new area of research.
Since alexithymia is nowadays considered in literature as an important complicating factor in both asthma and difficult asthma, a literature review that critically investigates the studies that reported on a possible relation between asthma and alexithymia is necessary. To the best of our knowledge, such a review has not yet been published.
The aim of the present study is to systematically review current literature with regard to (1) the prevalence of alexithymia in asthma; (2) possible associations between alexithymia and severity of asthma, asthma control and quality of life; (3) treatment and treatment outcome of alexithymia in asthma.

METHOD

A comprehensive literature search of the MEDLINE database on literature published from 1990 till July 2015 was conducted on alexithymia in asthma. The search was conducted by pairing the key words 'asthma' and 'alexithymia'. All fields were selected for a thorough search.
Studies meeting the following criteria were included in this review: (a) participants were adults above 18 years, (b) alexithymia was studied directly related to asthma, e.g. prevalence, a relation with severity of asthma, asthma control, quality of life or treatment of alexithymia in asthma (c) statistical analyses were well described and effect sizes could be calculated, (d) studies were published in English. Once an initial pool of articles was obtained, titles were screened on inclusion criteria. Abstracts from retained records were assessed to identify potentially relevant articles and duplicates were removed. For the remaining records full texts were obtained and articles were added to the search by cross-referencing of full texts. All eligible papers were submitted to close reading and were coded by two readers (L.P. and A.P.) on the following characteristics: (a) number of

participants, (b) asthma diagnosis of participants, (c) statistical analysis, (e) main findings concerning alexithymia, (f) control group, (g) prevalence, (h) severity, (i) quality of life. Effect sizes were calculated according to the analysis used, i.e. r for paired qualitative data, f^2 for ANOVA or multiple regression and *phi* for chi squared tests [29, 30]. According to Cohen's r criterion [30] correlations of $r \geq 0.10$ correspond with small, $r \geq 0.30$ with medium and $r > 0.50$ with large effect-sizes, the latter two are considered clinically relevant. Cohen's f^2 of $f^2 \geq 0.02$ corresponds with small, $f^2 \geq 0.15$ with medium and $f^2 > 0.35$ with large effect-sizes. Phi of ≥ 0.1 corresponds with small, *phi* ≥ 0.3 with medium and *phi* > 0.5 with large effect-sizes. The results of the search are summarized in table 1.

RESULTS

The search initially identified 71 hits. After applying the inclusion criteria mentioned above, the search resulted in 11 articles. There were no papers found by cross-referencing. The studies are described in table 1. Five of 11 articles used a control group, i.e. asthma and non asthmatic patients, students with asthma and students with who recently experienced an asthma attack, three studies of NFA and asthma patients of which one study also with a non asthmatic control group. The prevalence of alexithymia reported in the literature highly varied (table 1). From 0 to 19% in asthma patients compared to 24-36% in NFA patients. The two studies with the lowest prevalence had very low sample sizes: n = 44 (NFA), n = 40 (asthmatic control group) [34] and n = 25 [36]. Prevalence of alexithymia in asthma was higher compared to healthy controls and higher in patients with NFA compared to patients with asthma without NFA [32, 38-39].

Nine of 11 studies reported on a possible relation between alexithymia and severity in asthma. Seven out of these nine studies reported a significant positive relation between alexithymia and severity in asthma with large effect sizes. Two studies [33,36] reported no relation between alexithymia and severity in asthma, both with small effect sizes in contrast to the other seven studies. Two of 11 studies reported a relation between alexithymia and worse asthma control [33,36] (with respectively *phi* = 0.04 and r = 0.57 effect sizes) while one study found no relation [37] with asthma control (effect size not mentioned). Four of the 11 studies reported that alexithymia was related to poor quality of life [33, 35-37]. There were no studies on the possible effects of treatment of alexithymia in asthma.

Table 1. Alexithymia in Asthma

Study (first author)	Sample size and participants	Control Group	Statistical Analysis	Main Findings	Effect Size	Prevalence	Severity	Asthma Control	Quality of Life
Amore 2013 [9]	117 bronchial asthma patients in tertiary care	no	Hierarchical cluster analysis, two-tailed t-tests independent samples	Patients with poorer pulmonary function are more -alexithymic	large, r=0.59	14,70%	yes	no	no
Chung 2012 [31]	156 students (1 month) with an asthma attack 141 control asthma students	yes	Path analysis	Association between alexithymia and asthma severity	small, r=0.29	no	yes	no	no
Martinez-Rivera 2011 [32]	264 asthma patients 111 normal control	yes	ANOVA, logistic regression	-more alexithymia in asthmatics -more alexithymia in asthmatics with dysfunctional breathing	small, r=0.15 medium, r=0.46	no	no	no	no
Baiardini 2011 [33]	115 patients with moderate to severe asthma and comorbid rhinitis	no	Nonparametric tests, Chi square	Alexithymics have -no difference in GINA levels -worse asthma control -worse quality of life	small, phi=0.04 medium, r=0.31 small, r=0.15	19%	yes	yes	yes
Vázquez 2010 [34]	44 NFA, 40 matched asthmatic controls	yes	Student's t tests	There was no difference in alexithymia	small, r=0.19	9% NFA, 0% control group	no	no	no
Vázquez 2010 [35]	76 patients with moderate to severe asthma	no	Multiple linear regression	DIF is related to health care use DDF is related to quality of life (SF-36): -physical function -role physical -physical component score	medium, f2=0.22 large, f2=0.51 medium, f2=0.30 large, f2=0.42	no	yes	no	yes

Table 1. Alexithymia in Asthma (Continued)

Study (first author)	Sample size and participants	Control Group	Statistical Analysis	Main Findings	Effect Size	Prevalence	Severity	Asthma Control	Quality of Life
Chugg 2009 [36]	25 patients with moderate to severe asthma	no	Linear regression, ANOVA	Alexithymics have -worse asthma control -worse quality of life -no association with satisfaction with communication and hospitalizations	 large, r=0.57 large, r=-0.65 small, r=-0.27	12%	yes	yes	yes
Axelsson 2009 [37]	68 young adult asthmatics	no	Pearson and spearman correlations, multiple regression models	-alexithymia predicted mental dimension of HRQL -no relation between alexithymia and asthma control	nr no, r=0.007	no	no	yes	yes
Plaza 2006 [38]	50 NFA, 25 asthmatic controls, 25 non-asthmatic controls	yes	Chi^2 analyses, oneway ANOVA, Kruskal Wallis, Man Whitney	-more alexithymia in NFA -alexithymia is associated with more hospitalisations in NFA and non NFA	small, r=-0.26 small, r=0.25	12%	yes	no	no
Serrano 2006 [39]	179 NFA, 40 asthma controls	Yes	Chi^2analyses, unpaired t-tests	-more alexithymia in NFA -more regular use of inhaled and oral corticosteroids	large, r=0.81 nr	36% NFA 13% non NFA	yes	no	no
Feldman 2002 [40]	74 outpatients	No	Pearson and partial correlations	COM is related to decreased pulmonary function	Medium, r=0.30	no	yes	no	no

Abbreviations: nr=not reported, GINA, global Initiatitve for asthma; NFA, near fatal asthma; DIF, difficulty identifying feelings; DDF, difficulty describing feelings; HRQL, health related quality of life; COM, difficulty communicating feelings.

DISCUSSION

The current review shows a prevalence of alexithymia in asthma between 14,7% and 36% (table 1). This is high compared to the general population (13%) [41]. The study of Martinez et al. [32] confirmed that there is more alexithymia in asthma compared to control subjects without asthma. Moreover, the highest percentages of 24% [38] and 36% [39] are reported in NFA patients and the percentage of alexithymia is higher in NFA patients compared to asthma controls [38,39]. These results suggest that alexithymia is related to asthma in general and specifically to more severe asthma symptoms. Only two studies out of nine did not confirm this relationship, but these studies lacked sufficient power. There was also a relation between alexithymia and worse asthma control and lower quality of life.

The suggestion that alexithymia is a patient related factor in asthma is confirmed by the results of our review. Treatment of alexithymia in asthma could therefore be an opportunity in the management of asthma, especially for patients with more severe asthma like difficult asthma. However, no studies on the treatment of alexithymia in asthma are reported yet. Research on alexithymia in patients with other somatic diseases like coronary heart disease may give new possibilities on the treatment of asthma [42]. For instance, in coronary heart disease, group therapy reduces alexithymia for over two years. More importantly, patients with reduced alexithymia scores have better somatic outcomes that last over two years [42]. Several pathways are suggested in which the treatment of alexithymia can alter the prognosis of somatic disease [22]. When patients with alexithymia learn to give words to their feelings, learn how to discriminate between feelings and bodily sensations and move their attention more toward their inner experience, the cognitive processing of their feelings improves. This reduces prolonged states of emotional arousal [16], tonic physiological hyperarousal, unhealthy behaviour, biased perception and reporting of bodily sensations [22]. It therefore improves cardiovascular management and also reduces health care use [22]. There is no reason to suggest that these mechanisms will not work in (difficult) asthma patients.

Although psychotherapy is proven effective in treating alexithymia, as far as we know no treatment specifically designed to treat alexithymia in chronic conditions has been designed yet [13]. The importance of treating psychological symptoms is becoming more evident [2]. Specific psychotherapeutic interventions targeting alexithymia could possibly also be incorporated in pulmonary rehabilitation and thereby possibly further improve health outcome.

The strength of this paper is that we critically analysed all papers and calculated the effect sizes of the studies. This makes it easier to make cross study comparisons and it makes these conclusions more reliable. However, it should be mentioned that this systematic review only revealed 11 studies.

CONCLUSION

Alexithymia is highly prevalent in asthma and is related to severity of asthma symptoms, worse asthma control and lower quality of life. Treatment of alexithymia in patients with both asthma and high levels of alexithymia could be promising, however no empirical outcome-studies are available. More research is necessary on the role of alexithymia in asthma, the development of psychotherapeutic interventions in patients with both asthma and alexithymia and on outcome of such therapies.

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Chapter 6

Long lasting benefit of specialized pulmonary rehabilitation in patients with difficult asthma with high levels of psychological symptoms

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ABSTRACT

Introduction: Difficult asthma is a serious condition in which asthma symptoms are not responsive to standard treatment, which is possibly complicated by psychological symptoms. The (longterm) benefit of specialized pulmonary rehabilitation (PR) adjusted for the level of psychological symptoms at baseline, has not yet been studied in patients with difficult asthma.

Aims: (1) to evaluate if health related wellbeing and the level of psychological symptoms of patients with DA change during PR (2) to assess if there is an association between psychological symptoms and the effect of PR on health related wellbeing (3) to evaluate whether a possible benefit of PR persists at longitudinal follow-up.

Methods: 121 patients with difficult asthma participated in an inpatient PR programme for 12 weeks; At baseline (T0) and at discharge (T1), health related wellbeing (SGRQ) and psychological symptoms (SCL-90) were assessed. Health related wellbeing was also measured at three (T2), six (T3), 12 (T4) and 18 (T5) month's post-rehabilitation.

Results: After PR there were significantly lower SGRQ scores (t(116)=13,21, p<.000, d=1,22) and significantly lower SCL-90 total scores (t(116=6,89, p<.000, d=0,64). Adjusted for SCL-90 scores at baseline, SGRQ scores were still significantly lower compared to baseline scores at discharge, 3, 6, and 12 months follow up (F(185, 220)=2,14, p=.0024).

Conclusions: PR in DA patients results in significant short- and long-term improvement in health related wellbeing, also in DA patients with high levels of psychological symptoms.

INTRODUCTION

Patients with difficult asthma (DA) are severely impaired by the uncontrollable and invalidating nature of their asthma symptoms [1]. Although patients with DA represent a minority of the total asthma population, about 1.25 million people in the US and 2.5 million in Europe suffer from DA [2]. Patients with DA do not reach an acceptable level of control at step 4 or 5 of prescribed treatment [3]. The impact on health care is substantial, because of the many hospitalizations, emergency room (ER) visits and high medication use [3-6]. Standard treatment for patients with asthma - prescription of medication, avoiding asthma triggers and improving self-management strategies- is directed at maximizing symptom free periods and keeping the airways in the best possible physical state [2, 3]. DA is a condition in which symptoms are not responsive to this standard treatment [2, 7]. Specialized pulmonary rehabilitation (PR), an intensive rehabilitation programme of several weeks or months, is offered to patients with severe asthma including DA patients when pulmonary rehabilitation in the general hospital setting does not yield sufficient progress. PR is an intensive interdisciplinary treatment consisting of a combination of physical and psychological interventions. PR has been shown to be effective in improving health related wellbeing in severe asthma [8]. However evidence of benefits of PR specifically in DA patients, is scarce since outcome studies on PR are often focused on patients with severe asthma (including DA patients) and sometimes including COPD patients as well. To the best of our knowledge, no studies have been reported on treatment outcome for adult patients with DA specifically. Moreover, of the few studies that reported treatment outcome in severe asthma most focussed on the possible benefit immediately post-treatment, e.g. when patients are discharged from the PR programme rather than longitudinal outcome [9].

DA patients are at high risk for co-morbid psychological symptoms, including severe psychiatric disorders [10]. In an earlier study we found that over half of patients with DA had a psychiatric disorder [10]. Psychological symptoms are generally regarded as a complicating factor in the treatment of asthma [2]. The possible impact of co-morbid psychological symptoms on a possible benefit of PR for patients with DA has never been reported.

Therefore, the primary aim of the present study was to evaluate if health related wellbeing and the level of psychological symptoms of patients with DA change during PR and if patients may benefit from an intensive PR programme. The second aim was to assess if there is an association between psychological symptoms and (lack of) benefit of PR on health related wellbeing. The third aim was to evaluate whether a possible benefit of PR persists at longitudinal follow-up.

METHODS

Setting

This prospective study was conducted in 'Revant Centre for Pulmonary Rehabilitation', Breda, The Netherlands; a specialised tertiary asthma care centre that offers both inpatient and outpatient pulmonary rehabilitation. The rehabilitation itself consists of a comprehensive 3-months rehabilitation programme by an interdisciplinary team of healthcare professionals, including pulmonologists, physiotherapists, social workers and specialised health care psychologists [11]. Patients enter the PR after following a multidisciplinary assessment of four days. Patients have to be abstinent from smoking if they want to participate in the rehabilitation programme. Details of the PR of this institute have been described elsewhere [11].

Participants and procedure

From October 2006 until December 2013, 121 patients with DA were included in the specialised PR programme (T0). Treatment outcome was evaluated at discharge (T1), three months post PR (T2), six months post PR (T3), 12 months post PR (T4) and 18 months post PR (T5). Of these 121 patients (T0), 3% dropped out during the programme (i.e. did not complete PR). Therefore data analysis refers to 116 patients who ended the PR (T1); of these, 34 were lost to follow-up at 3 months (T2), 4 at six months (T3), 20 at 12 months (T4) and 7 at 18 months (T5) (table 1).

Measurements

Health related wellbeing (dependent variable) was assessed at T0, T1, T2, T3, T4 and T5 and was measured with the Saint George Respiratory Questionnaire (SGRQ), a commonly used 76 item questionnaire with three sub-domains, e.g. symptoms, activity and impact [12]. A summary score is calculated by empirically weighted item scores. Scores range from 0 (no impairment) to 100 (maximal impairment), thus higher scores reflecting poorer health status. A change of four points in summary score after PR is regarded a slightly efficacious change, eight points as a moderate change and 12 points as a very efficacious change. The SGRQ has proven to be a valid and reliable instrument [12] and was assessed at T0, T1, T2, T3, T4 and T5.

Psychological symptoms (independent variable) were measured at baseline (T0) and at discharge (T1) with the Symptom Checklist (SCL90) of Derogatis [13], a 90-item multi-dimensional self-report symptom inventory that measures

different symptoms of psychopathology. Total scores are used for the indication of psychological symptoms.
Physiological impairment was measured at T0 by airway obstruction: (FEV1, Forced Expiratory Volume in One Second) and after taking the deepest breath possible (FVC, Forced Vital Capacity), which is called FEV1%, and exercise performance was measured by the maximal power output on a cycle ergometer (W-max%) that has both good reliability and validity [14].
In addition, demographics and BMI were assessed at T0.

Ethical Principles

This study was review board exempt since all assessments are part of usual care provided by the rehabilitation centre and all data were anonymized. Patient's informed consent was obtained for the utilization of the data for research purposes.

Statistical Methods

All statistical analyses were performed with the IBM SPSS Statistics for Windows Version 22.0 [15].
Differences between patients who dropped out at different times of follow-up were analysed using independent samples t-tests for categorical variables and chi-square tests for dichotomous variables. Correlations between SGRQ baseline (T0) and SCL-90 sum-scores (T0), SGRQ after discharge (T1), SCL-90 after discharge (T1), the change (delta) between SGRQ T0 and T1 were evaluated using Pearson correlation ($P < 0.01$, two-tailed). Clinical relevance of the correlation was determined using Cohen's criterion [16]. According to this criterion correlations of $r \geq 0.10$ correspond with small, $r > 0.30$ with medium and $r > 0.50$ with large effect-sizes, the latter two are considered clinically relevant [16].
Possible changes of health status during the PR (T0-T1) were analysed using paired samples t-tests. Similarly, possible changes of psychological wellbeing (SCL-90 sum scores) during PR (T0-T1) were analysed using paired sample t-tests. Data are mean ± standard deviation and significance level, unless otherwise stated. Clinical relevance for effect sizes was determined using Cohen's d criterion [17]. According to this criterion correlations of $d \geq 0.20$ correspond with small, $d > 0.50$ with medium and $d > 0.80$ with large effect-sizes, the latter two are considered clinically relevant [17].
In order to evaluate the possible benefit during PR (T0 -T1), specifically if baseline SCL-90 scores were associated with the amount of change in SGRQ scores,

a stepwise multiple linear regression analysis was performed with difference of SGRQ summary scores between T1 and T0 as dependent variable and the T0 SCL-90 scores as independent variable [18], entered into the regression as first block. We adjusted for several parameters (age, gender, BMI, W-max%, FEV1%), which were entered as separate blocks, i.e. the second block age and gender, third BMI, fourth W-max and FEV1%. The adjusted R-square statistic was determined to indicate the proportion of explained variance, and the F-change statistic was determined to indicate the significance of adding separate blocks. Clinical relevance for R-square statistic was determined using Cohen's criterion [16]. According to this criterion a $R^2 \geq 0.010$ correspond with small, $R^2 > 0.059$ with medium and $R^2 > 0.138$ with large effect-sizes.
Finally, the possible longitudinal benefit of PR on health related health status (SGRQ summary scores) was evaluated using repeated measurements (GLM-ANOVA) with SGRQ scores at T0, T1, T2, T3, T4 and T5 as within-subjects factor [18] and SCL-90 baseline scores as between-subjects factor with Bonferroni correction for multiple testing. Because of high rates of drop-out which are not incorporated in repeated measures analyses (GLM-ANOVA), the analysis was repeated with 'linear mixed effect models', also with a Bonferroni correction for multiple testing. This analysis, which is interpreted as linear regression analyses, has the advantage that its statistical analysis includes all available data, and does not include listwise deletion.

RESULTS

The characteristics of patients with DA are shown in Table 1 at five intervals (T0-T5).
There were no significant differences for age, gender, BMI, FEV1%, W-max%, SCL-90 scores at baseline (T0), SCL-90 scores at discharge (T1) and SGRQ scores at all intervals (T0-T5) between patients who dropped out and who did not drop out during PR or during follow-up (T0-T5) as is shown in Table 1. The mean sum SGRQ and SCL-90 scores at baseline (T0) were 62,8 (SD: 16,5) and 168,9 (SD: 50,3), respectively. Correlations were significant with large effect sizes between SCL-90 scores at baseline (T0) and SCL-90 scores at discharge (T1) (r=0,64), between SGRQ at baseline (T0) and SGRQ at discharge (T1)(r=0,51) (Table 2). Correlations were significant with medium effect size between the SCL-90 at baseline and SGRQ at discharge (r=0,45), SGRQ at baseline (r=0,35) and SCL-90 at discharge (T1), SGRQ at discharge (T1) and SCL-90 at discharge (T1) (r=0,41). The correlation between SCL-90 baseline (T0) and SGRQ at discharge (T1) was significant with a small effect size (r=0,27).

At discharge (T1 versus T0), patients reported significantly lower SGRQ scores (mean 21,34 sd ± 1,62, *t*(116) = 13,21, p<.0001, d = 1,22, large effect size) as well as lower SCL-90 sum scores (mean 25,8 sd ± 3,7, *t*(116) = 6,89, p<.0005, d = 0,64, medium effect size, paired T-tests).
Comparing the decrease of SGRQ scores during PR (T0 and T1, dependent variable: SGRQ delta scores, independent variable: SCL-90 sum scores at T0) a multiple linear regression analysis showed no effect for SCL-90 sum scores at baseline, after adjustment for age, gender, BMI, W-max% and FEV1% (table 3). There was an independent effect of BMI at T0 on the SGRQ delta scores. Higher BMI was significantly associated with a larger decrease of SGRQ scores (R^2 0,09; p=0,04, medium effect size). Adding W-max% and FEV1% to the model increased the explained variance to 0.11 (R^2 0,11; p=0,04, medium to large effect size). SCL-90 sum scores at baseline did not contribute to the decrease of SGRQ scores.
In figure 1, the benefit during follow-up is shown of SGRQ scores using GLM-ANOVA with SCL-90 baseline (T0) as between subject factor. As can be seen, the SGRQ scores decreased significantly over time (F(5,20)=42,46, p<.0005, partial η^2=0,91, figure 1). Adjusted for SCL-90, SGRQ scores still decreased significantly over time (F(185, 20)=2,14, p<.0024, partial η^2=0,95). Between baseline (T0) and SGRQ scores at discharge (T1) there was a decrease of 23,1 points, which is a clinically relevant change [12^2. At follow up, at three months (T2), six months (T3), 12 months (T4) and 18 months (T5) there was a slight increase of the SGRQ sum scores but at 18 months follow-up the difference between T4 and T0 was still 15,9 points on the SGRQ, which is a significant and clinically relevant change [12]. T5 and T0 was still 15,4 points, which is not a significant (p=0.62) but still a clinically relevant change. Post hoc analyses with a Bonferroni adjustment revealed that SGRQ sum scores significantly decreased from T0 to T1 (p=0.002), T2 (p=0.004), T3 (p=0.005), and T4 (p=0.027). SGRQ decreased from T0 to T5 however this was not significant (p=0.088). The slight increase from T2 to T5 was not significant. The drop out rate from T0 to T5 was over 50%, which is not incorporated in repeated measures analyses. We therefore repeated the analysis with a linear mixed effect model. This analysis showed the same effects, which makes it reliable to report the repeated measures analyses. The SCL-90 scores at baseline did not significantly predict the change of SGRQ scores.

Table 1. Characteristics of patients with difficult asthma

	T0 (N=122)					T1 (N=116)					T2 (N=81)					T3 (N=66)					T4 (N=50)					T5 (N=42)				
	N	%	Mean	SD	Range	N	%	Mean	SD	Range	N	%	Mean	SD	Range	N	%	Mean	SD	Range	N	%	Mean	SD	Range	N	%	Mean	SD	Range
Demographics																														
Female	87	71,3				83	71,6				56	69,1				50	75,8				37	74				32	76			
Age			47,8	14,2	61			47,7	14,4	61			48,4	14,0	61			49,4	13,1	57			51,7	11,7	46			52,9	11,6	46
BMI			30,5	6,4	28,4			30,6	6,4	28,4			30,4	6,1	27,8			30,4	6,2	27,8			30,3	6,2	27,8			30,6	6,3	27,8
Physiological measures																														
FEV1 %			84,0	24,0	107			83,9	23,9	107			83,7	24,4	104			84,6	23,2	104			87,1	21,2	88			84,4	21,6	88
W-max %			68,1	23,6	114			68,2	23,9	114			67,3	23,7	114			69,6	22,9	114			72,5	22,8	114			70,4	22,1	96
Psychological measures																														
SCL-90* T0			169,0	50,3	280			168,9	49,6	280			166,0	47,6	280			169,2	49,0	280			167,7	49,4	280			164,9	41,2	179
SCL-90* T1								143,0	46,3	271			142,4	47,1	271			144,0	47,9	266			145,1	51,8	266			141,1	40,3	166
SGRQ T0			62,9	16,5	72			62,7	16,6	72			62,7	16,9	72			63,2	16,9	72			61,6	17,6	72			64,0	17,0	72
SGRQ T1								41,2	18,9	81			40,8	18,6	78			40,2	19,1	78			40,8	18,2	73			41,3	17,6	72
SGRQ T2													41,8	20,4	80			41,4	20,9	80			41,4	20,2	73			41,8	20,0	73
SGRQ T3																		44,4	22,2	83			43,9	22,4	76			44,9	21,1	73
SGRQ T4																							47,2	23,2	89			48,4	22,0	89
SGRQ T5																												49,4	23,9	84

*SCL-90 is not recoded to 0 in the Netherlands

Abreviations: BMI, Body Mass Index; FEV1%, forced expiratory volume in 1 second predicted; W-max%, maximal power output on cycle ergometer predicted; SCL-90, Symptom Checklist;

SGRQ, Saint George Respiratory Questionnaire

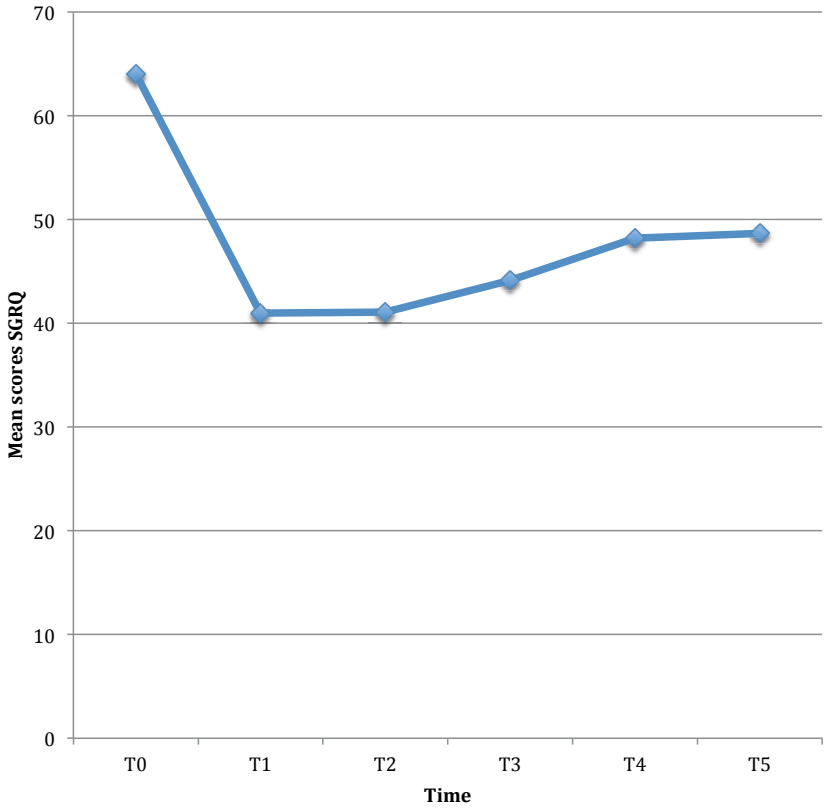

Figure 1. SGRQ mean scores and repeated measures for DA patients from baseline to 18 months post PR

Table 2. Correlations between psychological symptoms, health related wellbeing at baseline, at discharge and between baseline and discharge (N=116)

	SCL-90 T0	SCL-90 T1	SGRQ T0	SGRQ T1
SCL-90 T0	.	.	.	.
SCL-90 T1	0,64*	.	.	.
SGRQ T0	0,45*	0,35*	.	.
SGRQ T1	0,27*	0,41*	0,51*	.
SGRQ delta	0,11	-0,12	0,39*	-0,59*

* Correlation is significant at $p < 0.01$ level, two tailed
Abbreviation: SCL-90, Symptom Check List; SGRQ, St. George's Respiratory Questionnaire; T0, baseline; T1, at discharge; delta, the difference between T0 and T1

Table 3. Stepwise multiple linear regression analysis with the delta of patients' perceived wellbeing (SGRQ) as the dependent variable and baseline SCL-90 scores as independent variable, adjusted for age, gender, BMI, FEV1% and Wmax% (N=116)

		95% CI						
	Beta	**Low**	**Upper**	***p***	**R square**	**Adj R square**	**F change**	**Sig. F. Change**
I					0,01	0,00	1,51	0,22
SCL-90 baseline	0,11	-0,03	0,11	0,22				
II					0,03	0,00	1,14	0,33
SCL-90 baseline	0,12	-0,02	0,11	0,21				
age	-0,14	-0,39	0,06	0,14				
gender	0,03	-5,80	8,46	0,71				
III					0,09	0,05	6,68	0,01*
SCL-90 baseline	0,06	-0,05	0,09	0,55				
Age	-0,17	-0,43	0,01	0,07				
Gender	0,00	-6,77	7,25	0,95				
BMI	0,25	0,16	1,18	0,01*				
IV					0,11	0,06	1,49	0,23
SCL-90 baseline	0,07	-0,04	0,09	0,49				
age	-0,16	-0,41	0,03	0,09				
gender	0,04	-5,59	8,89	0,65				
BMI	0,25	0,15	1,20	0,01*				
FEV1%	0,13	-0,06	0,25	0,24				
W-max%	0,06	-0,13	0,21	0,63				

* Independent variable is significant at the 0.05 level (2-tailed)
Abreviations: BMI, Body Mass Index; FEV1%, forced expiratory volume in 1 second predicted; SCL-90, Symptom Checklist;
SGRQ, Saint George Respiratory Questionnaire; W-max%, maximal power output on cycle ergometer predicted;

DISCUSSION

The primary outcome of this study was that both health related wellbeing and psychological symptoms improve significantly with a clinically relevant effect size in patients with DA during PR. Second, in contrast to what was expected, the level of psychological symptoms at baseline was not related to the progress made on health related wellbeing during PR. The third outcome was that the beneficial effect of PR persisted over 12 months post PR.

Patients were highly impaired at the start of rehabilitation, which is represented in very low health related wellbeing (high SGRQ scores), which is even lower compared to patients with severe asthma with frequent exacerbations [19]. Similarly, the level of psychological symptoms was very high, approaching norm

scores of the outpatient psychiatric population in The Netherlands [13]. Although patients had high levels of psychological symptoms and psychological symptoms are seen as complicating factors in the treatment of DA [7], these patients did benefit from an intensive multidisciplinary specialized PR programme. The most likely explanation is that since there was a significant amount of psychological interventions in the specialized PR programme, psychological symptoms were treated well enough not to intervene with the "physical elements" of the PR programme, making this programme suitable for patients with DA. This could also explain the improvement in psychological symptoms during PR. Therefore we conclude that the severity of psychological symptoms does not have to be a contra-indication for PR and does not require treatment before PR starts. However, because DA patients with severe psychiatric disorders were excluded from this study, it is difficult to generalize these findings to all DA patients.

This study has both its strengths and limitations. One of the strengths of our study is the measurement of not only short term but also long term benefits of PR in a group of DA patients (reflecting a sub-group of asthma patients with very severe symptoms difficult to treat), which are often excluded from studies. It was also a relatively large population of well-defined DA patients. Although the drop-out rates were high during the follow-up of 12 months, the extra mixed models analysis which confirmed the repeated measures analysis, made our results at follow up more reliable. A limitation of the study was that patients were only followed on health related wellbeing after discharge. For example data of hospitalisations, exacerbations, possible death, use of medication, the level of psychological symptoms during follow-up were unknown. In addition, pulmonary function and exercise performance was only part of our analyses at baseline with no data after discharge [2]. Therefore we could not adjust for physiological improvement during and after PR, which also might influence psychological and health related wellbeing. Also, psychological interventions during PR were individualized for each patient making it impossible to correct for the quality and quantity of psychological interventions during PR. In addition, data on possible additional physical and psychological interventions during follow up were not available. Since PR occurs in a highly specialized setting treating severely ill patients, a control group or RCT for obvious reasons was not possible.

CONCLUSION

PR may be considered as a beneficial programme with long-lasting effect to increase health related wellbeing of DA patients, even in cases with high levels of psychological symptoms before treatment.

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Chapter 7

Summary and general discussion

SUMMARY OF MAIN FINDINGS

Although asthma is a well treatable chronic disease, about 5% of patients does not respond well to regular (pharmacological) treatment and suffers from difficult asthma (DA) [1]. These patients are seriously restricted in their daily activities, consume a significant part of medical assistance, suffer from frequent exacerbations, are prone to medical complications [2-4], and have low quality of life [5]. DA constitutes a relatively heavy burden on society [6]. Factors causing DA are not well understood. There are indications that – apart from pathophysiological factors—psychological factors may play a role in the development and maintenance of DA. Although the widely accepted existing recommendations for treating general asthma following GINA criteria also incorporate a psychological attitude, empirical support for this line of reasoning seems scarce.

The main aim of this thesis was to gain a better understanding of DA from a psychological point of view. Specifically two concepts were studied in relation to DA, i.e. psychiatric symptomatology /syndromes and alexithymia. These two concepts are considered complicating factors in both worldwide management guidelines and clinical practice of DA.

A PSYCHOLOGICAL APPROACH IN UNDERSTANDING DIFFICULT ASTHMA

Psychopathology

Several available empirical studies confirmed that there was a higher *prevalence* of psychiatric symptoms and syndromes in DA compared to the general population, as is described in ***Chapter 2***. Moreover patients with DA and co-morbid psychiatric symptoms experienced more asthma hospitalizations and exacerbations compared to patients with DA with less psychiatric symptoms [7]. Literature suggested a possible role of psychiatric symptomatology in DA, but was rather inconclusive and the direction of the relation between psychiatric symptomatology and DA remained speculative.

In ***Chapter 3*** we studied the intensity of psychiatric symptoms in patients with DA. The intensity of psychiatric symptoms was higher compared to the general population and close to that found in outpatient psychiatric populations. In addition, the intensity of psychiatric symptoms had a stronger association with health related wellbeing in patients with DA compared to well-known asthma

related parameters like age, gender, BMI, airway obstruction and exercise performance.
An interesting and unexpected finding was the lack of difference of the intensity of psychiatric symptoms and perceived wellbeing between males and females with DA. In general, females tend to report psychiatric symptoms more often compared to men [8]. One would expect to find a similar difference in the present sample especially since female patients with asthma also tend to report more asthma symptoms and worse health related wellbeing compared to male patients, despite having similar or better lung function [9]. Therefore in assessing and treating patients with DA, we should not only consider high intensity of psychiatric symptoms in females but also consider high intensity of psychiatric symptoms in males.

In ***Chapter 4*** we studied psychiatric problems at syndrome level in patients with DA. Over half (54,9%) of patients with DA had one or more psychiatric disorder and 89,3% of these disorders was previously unrecognized. More specifically, 49% of all patients with DA had a major mental disorder. This prevalence was higher in comparison to the 31–34% reported [10, 11] in asthmatic outpatients, including both 'normal' asthmatic patients and patients with difficult asthma. The prevalence of 49% of major mental disorders was also substantially higher in comparison to that of the general population in the USA (26.6%) [12] and in The Netherlands (18%) [13]. Similarly, the prevalence of personality disorders in DA of 19.6% in the current study was also substantially higher compared to the general population in the USA (9%) [14] and in The Netherlands (13.5%) [15].

We may conclude from the two empirical studies that psychopathology at both symptom and syndrome level is highly prevalent in DA. Especially the high prevalence at syndrome level is important because it emphasizes the severity of psychopathology in DA. Psychiatric *symptoms* can be subclinical but psychiatric syndromes may influence everyday life and hence warrant specific treatment. Another important finding was that psychiatric symptoms appeared to have a stronger association with perceived wellbeing compared to age, gender, BMI, airway obstruction and exercise performance. Health related wellbeing is widely accepted as an important marker of progress made by a patient in rehabilitation [16]. Therefore diagnostics into and treatment of psychiatric symptoms and syndromes appeared to be important in patients with DA.

Alexithymia

Besides psychiatric symptoms and syndromes, alexithymia (affective-cognitive emotion-regulation) is also considered a major complicating factor in DA [17]. Most patients diagnosed with DA seem not able to adequately perceive signals of forthcoming exacerbations -emotions or physical signs- and hence over- or underreact to these signals [18, 19]. This over- or under perception can be a consequence of a psychological condition named 'alexithymia'. As such the introduction of the concept of "alexithymia" may contribute to a better understanding of the mechanisms resulting in DA and provide us with treatment opportunities for DA. Our review of the available empirical literature in ***Chapter 5*** showed a high prevalence of alexithymia in asthma: between 14,7% and 36%, which was higher compared to the general population (13%) [20]. This review also suggested that alexithymia is related to asthma in general and specifically to more severe asthma symptoms. There was also a relation between alexithymia on the one hand and worse asthma control and lower quality of life on the other hand. The suggestion that alexithymia is a patient related factor in asthma, and may possibly be related to worse asthma [21, 22] seemed to be confirmed by the review.

Specialized pulmonary rehabilitation

As psychological factors may play a role in the etiology and maintenance of DA, we studied the outcome of existing well-established rehabilitation programs consisting of both physical and psychological elements –a multidisciplinary treatment. Specialized health care psychologists assessed all patients and treated positive cases with individualized psychological treatment, which consisted also of group-based psychosocial counseling sessions. Our study in ***Chapter 6*** in DA patients demonstrated that such specialised pulmonary rehabilitation programs might contribute to improved health related wellbeing in patients with DA and that this improvement might persist at longitudinal follow up, i.e. 12 months post-rehabilitation. Health related wellbeing improved significantly along with significant improvement of psychiatric symptoms during rehabilitation. Due to limitations of the design no data were available with regard to possible changes in exacerbation frequency.

Based on the results of our studies in ***Chapter 2*** and ***3***, wherein psychiatric symptoms seemed to pose as complicating factors in the treatment of DA [7], we hypothesized that the level of psychiatric symptoms at the start of the rehabilitation would negatively influence outcome of the rehabilitation. Specifically, we hypothesized that the improvement during rehabilitation would

be smaller if the level of psychiatric symptoms was higher at the start of the rehabilitation. In contrast to what we expected, there was no relation between psychiatric symptoms at baseline and the progress made on health related wellbeing during rehabilitation. It is most likely that since there was a significant amount of psychological interventions in the specialist PR programme, psychiatric symptoms were treated well enough not to interfere with the "physical elements" of the PR programme, making this programme suitable for patients with DA.

GENERAL DISCUSSION

THEORETICAL AND POSSIBLE CLINICAL IMPLICATIONS

At the start of this thesis a potential role of psychological factors in the etiology and maintenance of DA was only confirmed by a small amount of papers on psychological subjects in DA. This thesis tried to complement existing literature on psychopathology in DA and to create an empirical base for existing management programs for DA. The main aim of this thesis was to gain a better understanding of DA from a psychological point of view.

Existing scarce literature confirmed the presence of high intensity of psychiatric symptoms in DA (***Chapter 2)***. Our research also confirmed this high intensity of psychiatric symptoms and syndromes (***Chapter 3 and 4***). Besides anxiety and depression, other psychiatric symptoms and syndromes were also present in DA. It is therefore advisable to study the broad spectrum of psychiatric syndromes in DA. For example, specifically obsessive compulsive personality disorder was relatively frequent in DA.

Although this thesis confirmed the high frequency of psychiatric symptoms and syndromes in DA, its role in the etiology and maintenance of DA remains uncertain. The direction of the relation between psychiatric symptoms and syndromes may be bi-directional; DA may result in psychiatric symptoms and syndromes and in alexithymia and/or vice versa. More research, in particular longitudinal research also involving other psychological factors like patient compliance, coping strategies, social economic status and less known factors like resilience and attachment styles- on psychological factors in DA and specifically path analyses are necessary to create an empirical base of theories on psychological factors in the etiology and maintenance of DA. For future research combining this psychological approach with a pathophysiological approach, a biopsychosocial approach, would probably give even more insight into the etiology and maintenance of DA. This thesis did create an empirical base for such a theory because we provided evidence that psychiatric symptoms and

syndromes are highly prevalent in DA. Future research may focus on the role and direction of psychological factors, best in combination with pathophysiological, in DA.

The question whether treatment of DA also treats psychiatric symptoms and syndromes and/or vice versa is interesting for future clinical research. In general, psychiatric symptomatology is more prevalent in women, in DA the intensity was equally high in both men and women (***Chapter 3***). Although screening of psychopathology is advised at an early stage of asthma in GINA-guidelines, psychiatric symptoms and syndromes are still easily overlooked, even in highly specialized care: up to 80% of the DA patients who suffered from a psychiatric syndrome was undiagnosed at time of assessment. This is probably because of the rather dramatic somatic manifestation of the disease, a definition that is based on pharmacological treatment and a fear of stigmatizing in both the eyes of patient and doctor.

Psychological factors, i.e. psychiatric symptoms and syndromes and alexithymia, play an important role in health related wellbeing in DA. However, our thesis did not confirm psychiatric symptoms being a complicating factor of successful specialized pulmonary treatment. Although psychiatric symptoms seemed to occur frequently in DA, the improvement of health related wellbeing during rehabilitation suggests that psychiatric symptomatology is no contra-indication for specialized rehabilitation. Psychiatric symptoms decreased during rehabilitation. Future research should show if this is a result of the specific multidisciplinary treatment incorporating also psychological interventions. It is also still uncertain whether psychiatric symptoms are complicating factors in non-specialized care. This again also questions the role of psychiatric symptoms in DA and thus causality. It is important to specifically study whether the psychological interventions in specialized pulmonary rehabilitation prevent psychiatric symptoms interfering with treatment outcome or whether psychiatric symptoms are just a comorbid condition, which is more frequent in DA but does not complicate treatment. In addition, if specific interventions prevent interference, these could possibly be integrated in an earlier phase of asthma treatment.

For clinical practice it is important to consider treating these comorbid psychiatric symptoms and syndromes *after* or concurrent with specialized pulmonary rehabilitation rather than *before.* Treatment of psychiatric symptoms and syndromes can be considered after rehabilitation because they seemed no contra-indication for rehabilitation. Patients do need treatment because of the relation with poorer health related wellbeing in DA. In addition, although there

was a significant reduction of psychiatric symptoms during rehabilitation, it is unknown if these are reduced to a subclinical level. This needs to be addressed in future research.
Referral to easy accessible psychological care in an early stage in Primary Care, like the POH-GGZ – a nurse-practitioner specialized in mental health care - in The Netherlands does seem advisable. However, once DA has been diagnosed, psychiatric evaluation should certainly be included in the standard medical examinations of patients with DA. Referral to a specialized health care psychologist or psychiatrist is advised, already at an early phase in asthma-care, in the hospital outpatient setting and not just until a patient has been referred to a specialized pulmonary rehabilitation center. The under-diagnosis and hence under-treatment of both psychiatric symptoms and syndromes and the possible role of alexithymia in DA should be minimized in order to reduce as much as possible the burden of patients with DA and their environment.
Probably because of the dramatic manifestation of asthma symptoms in DA, it is difficult to discriminate between psychiatric and asthma symptoms, not only for patients but also for pulmonologists. Awareness of the possible presence of psychiatric symptoms and syndromes may sensitize professionals working with asthma patients to overcome this problem. In addition, at least in The Netherlands, there is still a stigma on psychiatric diseases. This may result in unwillingness to acknowledge and accept psychiatric symptoms [23].

The role of alexithymia should also be taken into account in DA, as it makes it more difficult for patients not only to differentiate between emotions and bodily sensations but also to communicate their physiological and psychological/ psychiatric symptoms to health care professionals. Alexithymia should therefore also be considered when interpreting the reporting of symptoms by patients with DA. Communicating their symptoms, and understanding them, is more difficult for these patients and could obscure the assessment of the clinical condition and hence complicate treatment.
Alexithymia appeared to be present in a substantial part of patients with DA and could be an explanation of the clinical observation that DA patients often cannot detect early warning symptoms preceding exacerbations or mistake asthma symptoms for emotions and over-report symptoms. As a consequence, at least in a number of patients, alexithymia might partially maintain the DA-symptomatology. Awareness of the possible presence of alexithymia by health care professionals and patients may improve treatment (***Chapter 5)***, by incorporating (existing) therapies involving treatment of alexithymia. Such a

therapeutic approach should differentiate between patients that over- and those that under-perceive signs and symptoms of asthma. A 'new' area of research exploring the role of alexithymia in the etiology and treatment outcome of DA is recommended. When higher levels of alexithymia are present in a DA patient, a multidisciplinary approach (outpatient or in a rehabilitation center) is probably the best setting to diagnose and treat this problem because psychological factors and physiological factors can be unraveled and the patient can learn how to differentiate between emotions and feelings versus asthma symptoms.
Treatment of alexithymia in asthma –and especially in DA- could be an opportunity in the management of asthma, because it is known that alexithymia is important in the etiology and maintenance of other somatic chronic diseases [24]. Moreover, in these chronic conditions, treatment targeting at better perception of physical and emotional signals resulted in less symptoms [24]. Until now, no studies on the treatment of alexithymia in asthma have been reported.

We propose a different approach towards the understanding, assessment and treatment of asthma/DA. Although GINA tries to bridge between psyche and soma, in our view, a more integrated view of asthma/DA needs to be developed. Such a view should increase awareness at an early stage whether psychiatric symptoms and syndromes and alexithymia are involved in patients with asthma/DA. As a consequence, this should result in a referral at an early stage to a physician, psychiatrist or psychologist or a combination of health care professionals for adequate treatment. Already in Primary Care, all asthma patients who do not respond adequately to the first steps of the GINA guidelines should receive a psychological assessment by the nurse practitioner of the GP. If psychiatric symptoms seem to be prevalent, referral to a psychologist (within Primary Care) is advocated with additional focus on the possible existence of alexithymia. If the patient is still not responding to this (multidisciplinary) treatment, referral to a pulmonologist and medical psychologist of a hospital is advisable for further diagnostics. If psychiatric symptoms and/or alexithymia are predominant aspects of the asthma symptoms, referral to a pulmonary rehabilitation center is advisable where a more integrated treatment approach is readily available, as they target physical aspects, psychiatric symptoms and syndromes and alexithymia.

THEORETICAL AND PRACTICAL LIMITATIONS:

DIFFICULT TO TREAT AND DIFFICULT TO STUDY

Complicating factors

DA, by definition, is an asthma subgroup, which is difficult to *treat.* An explanation for the difficulty of treating DA, as shown by this thesis, is the possible role of psychiatric symptoms, syndromes and alexithymia. Literature on psychopathology in DA was scarce which made a psychological approach - research on psychiatric symptoms, syndromes and alexithymia - to DA appear to be a rather new focus.

DA itself also appeared to be a difficult subgroup to *study*. The definition of DA is based on pharmacological treatment results instead of specific disease characteristics. DA is as a result a heterogeneous group consisting of several subgroups of patients with different characteristics. It is for instance questionable whether NFA (near fatal asthma), a subgroup of DA, is comparable to brittle asthma – another subgroup. One may speculate that DA is too heterogeneous. However, it is a group of patients that GP's and pulmonologists see in their practice with a great burden for patients themselves and society. The problem of heterogeneity also made it difficult to compare the treatment outcome of the few studies we found on DA.

Another complicating factor in our thesis was the rather unknown concept of alexithymia in both asthma and DA. Only few studies investigated the role of alexithymia in asthma and no specific studies studied alexithymia in the etiology of DA. In addition, no studies reported on the effect of treating alexithymia in asthma or DA.

The probable presence of alexithymia in asthma also causes a specific problem of studying asthma/DA. Patients with alexithymia have difficulty in recognizing both emotional and bodily sensations and putting these into words. This makes it difficult to adequately rely on self-report measures regarding feelings and sensations. This could in turn have influenced studies with self-reports on somatic and mental health. As a result, prevalence figures of psychopathology in asthma/DA patients assessed by self-report instruments should be interpreted with caution. A possible way to overcome misinterpretation of psychiatric symptomatology is the use of a standardized psychiatric interview. During this interview, the health care professional will gain more insight whether the (high or low) levels of symptoms is partly to be explained by alexithymia.

Another complicating factor that needs to be mentioned and will always – by definition - influence research of DA, is the use of corticosteroids. Corticosteroids

are well known to have major psychotropic side effects, especially in chronic high doses, which is often the case in DA [25, 26]. Psychiatric distress is heightened in patients with severe prednisone dependent asthma [25] and the use of oral corticosteroids is related to lower quality of life [26]. A possible independent effect of this medication on major mental disorders should be taken into account [27] in future studies.

Strengths and limitations

This thesis has several strengths and limitations. A first strength is that we studied our patient group with only limited exclusion criteria. As a consequence however, this resulted in a heterogeneous group in which it is questionable whether results can be generalized to all DA patients in all settings. In addition, patients with severe psychopathology that could interfere with treatment were excluded in the three empirical studies in this thesis. This also limits generalizability.

Another strength is that we used well-validated instruments, including interviews for diagnosing psychiatric syndromes for both major mental disorders and personality disorders.

This thesis studied both the intensity of psychiatric symptoms and the presence of psychiatric syndromes. A limitation is that the use of self-reports could have resulted in a bias because of probable high intensity of alexithymia in DA. However, the interviews also showed high frequency of psychiatric syndromes, suggesting that indeed DA patients suffer from high intensity of psychiatric symptoms, a finding also found in other studies. In addition, as mentioned above, patients with severe psychopathology which could interfere with treatment were excluded, which could also diminish the frequency of psychopathology in our samples. This therefore emphasizes that patients with DA suffer from high intensity of psychiatric symptoms.

We studied the relation between the intensity of psychiatric symptoms and specialized treatment. In this naturalistic study, however, psychological interventions were individualized resulting in (a) not knowing if and which interventions resulted in the best outcome, and (b) not knowing if these interventions prevented psychiatric symptoms from interfering with treatment outcome. In addition, we combined psychological measures with physiological measures in a limited way. In future research it is important to broadly measure on both dimensions. Since RCT's are less desirable in the research of these patients, single case designs could provide further insight in the differing types of DA patients.

There is a proportion of patients with DA who do not report psychiatric symptoms and/or alexithymia. This thesis did not clarify which factors in these patients without high intensity of psychiatric symptoms and alexithymia are complicating DA. Therefore more research on DA is necessary discriminating between different types of DA patients in order to find out which interventions are preferentially applicable for which patients. As a result, a more differentiated treatment approach could become more effective.

CONCLUSIONS

This thesis provides empirical evidence that psychiatric symptoms and syndromes are highly prevalent and often unrecognized in DA, irrespective of gender. Specialized pulmonary rehabilitation may be beneficial for patients with DA with long lasting effect on health related wellbeing. Psychiatric symptoms are no contra-indication for treatment and improve also during rehabilitation. Early referral for psychological assessment and treatment is recommended for patients with DA. Alexithymia is probably also highly prevalent in asthma and DA and needs further research. Future research should use a more integrated approach including both psychological and pathophysiological aspects.

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S

Samenvatting

Summary

SAMENVATTING VAN DE VOORNAAMSTE BEVINDINGEN

Normaliter is astma een goed behandelbare chronische ziekte waarbij desondanks 5% van de patiënten niet goed reageert op reguliere (farmacologische) behandeling en lijdt aan moeilijk behandelbaar astma (Difficult Asthma: DA) [1]. Deze patiënten hebben zeer ernstige beperkingen in hun dagelijkse bezigheden, ze consumeren een significant gedeelte van de door astma patiënten gebruikte medische hulp, lijden aan frequente exacerbaties, zijn vatbaar voor medische complicaties [2-4] en ze hebben een lage kwaliteit van leven [5]. DA vormt een relatief zware last voor de maatschappij [6]. Factoren die DA veroorzaken zijn tot nog toe onduidelijk. Er zijn indicaties dat –buiten somatische factoren- psychologische factoren mogelijk een rol spelen in de ontwikkeling en het in stand houden van DA. Hoewel de wereldwijd geaccepteerde aanbevelingen volgens GINA criteria voor het behandelen van astma in het algemeen ook een psychologische attitude bevatten, is empirische onderbouwing van deze redenering beperkt.

Het hoofddoel van deze thesis is het beter begrijpen van DA vanuit een psychologisch oogpunt. Specifiek worden twee concepten bestudeerd in relatie tot DA, te weten psychiatrische symptomatologie/syndromen en alexithymie. Deze twee concepten worden beschouwd als complicerende factoren in DA in zowel wereldwijde management richtlijnen en in de klinische praktijk.

EEN PSYCHOLOGISCHE BENADERING IN HET BEGRIJPEN VAN MOEILIJK BEHANDELBAAR ASTMA (DA)

Psychopathologie

Verschillende beschikbare empirische studies bevestigden een hogere *prevalentie* van psychiatrische symptomen en syndromen in DA in vergelijking met de algemene populatie, zoals beschreven is in ***Hoofdstuk 2***. Patiënten met DA en comorbide psychiatrische symptomen ervoeren bovendien meer astma hospitalisaties en exacerbaties in vergelijking met patiënten met DA met minder psychiatrische symptomen [7]. De literatuur suggereerde daarnaast dat er een mogelijk rol was voor psychiatrische symptomatologie in DA, maar dit bleef nogal onduidelijk en de richting van de relatie tussen psychiatrische symptomatologie en DA bleef speculatief.

In ***Hoofdstuk 3*** bestudeerden we de intensiteit van psychiatrische symptomen in patiënten met DA. De intensiteit van psychiatrische symptomen was hoger

in vergelijking met de algemene bevolking en kwam dichtbij de intensiteit die gevonden wordt in ambulante psychiatrische populaties. De intensiteit van de psychiatrische symptomen had bovendien een sterkere associatie met welzijn gerelateerd aan de medische conditie in patiënten met DA vergeleken met bekende parameters als leeftijd, sekse, BMI (Body Mass Index), luchtwegobstructie en bewegingsprestaties. Een interessante en niet verwachte bevinding was het gebrek aan verschil in de intensiteit van psychiatrische symptomen en welzijn gerelateerd aan de medische conditie tussen mannen en vrouwen in DA. In het algemeen hebben vrouwen een grotere neiging tot het rapporteren van psychiatrische symptomen in vergelijking tot mannen [8]. Verwacht werd een gelijk verschil te vinden in de huidige populatie, zeker aangezien vrouwen met astma ook meer astma symptomen en slechter welzijn gerelateerd aan de medische conditie neigen te rapporteren in vergelijking met mannelijke patiënten, ongeacht vergelijkbare of betere longfunctie [9]. Derhalve zouden we in het onderzoeken en behandelen van patiënten met DA, niet alleen bij vrouwen maar ook bij mannen hoge intensiteit van psychiatrische symptomen moeten overwegen.

In ***Hoofdstuk 4*** bestudeerden we psychiatrische problemen op syndroom niveau in patiënten met DA. Meer dan de helft (54,9%) van de patiënten met DA had een of meer psychiatrische stoornissen en 89,3% van deze stoornissen was eerder niet onderkend. Specifiek had 49% een psychiatrische stoornis. De prevalentie was hoger dan de 31-34% die gevonden wordt in astmatische ambulante patiënten [10,11], waarbij zowel 'gewone' astmatische patiënten in de populatie zitten als patiënten met DA. De prevalentie van 49% psychiatrische stoornissen was ook substantieel hoger in vergelijking met die van de algemene populatie in de USA (26,6%) [12] en in Nederland (18%) [13]. Evenzo was de prevalentie van persoonlijkheidsstoornissen van 19,6% in de huidige studie ook substantieel hoger dan die van de algemene populatie in de USA (9%) [14] en in Nederland (13,5%) [15].

Uit de twee empirische studies mogen we concluderen dat de prevalentie van psychopathologie zowel op symptoom als syndroomniveau hoog is in DA. Vooral de hoge prevalentie op syndroomniveau is belangrijk omdat dit de ernst van de psychopathologie in DA benadrukt. Psychiatrische *symptomen* kunnen subklinisch zijn maar psychiatrische syndromen beïnvloeden het alledaagse leven en behoeven derhalve specifieke behandeling hiervoor. Een andere belangrijke bevinding was dat psychiatrische symptomen een sterkere relatie met welzijn

gerelateerd aan de medische conditie hadden vergeleken met leeftijd, sekse, BMI, luchtwegobstructie en bewegingsprestaties. Welzijn gerelateerd aan de medische conditie wordt breed geaccepteerd als een belangrijke marker van vooruitgang voor een patiënt binnen de longrevalidatie [16]. Diagnostiek en behandeling van psychiatrische symptomen en syndromen bleek derhalve belangrijk in patiënten met DA.

Alexithymie

Naast psychiatrische symptomen en syndromen wordt alexithymie (affectieve-cognitieve emotieregulatie) ook beschouwd als een belangrijke complicerende factor in DA [17]. De meeste patiënten die gediagnosticeerd zijn met DA lijken niet in staat om adequaat signalen waar te nemen van aankomende exacerbaties en dus teveel of te weinig reageren op deze signalen [18,19]. Dit teveel of te weinig waarnemen is een onderdeel van een psychologische conditie die 'alexithymie' wordt genoemd. Als zodanig kan de introductie van het concept 'alexithymie' bijdragen aan een beter begrip van de mechanismen die resulteren in DA en ons behandelmogelijkheden voor DA geven. In ***Hoofdstuk 5*** toonde de beschikbare empirische literatuur een hoge prevalentie van alexithymie aan in astma: tussen de 14,7% en de 36%, wat hoger is in vergelijking met de algemene populatie (13%) [20]. De uitkomsten van de review suggereerden dat alexithymie gerelateerd is aan astma in het algemeen en specifiek aan meer ernstige astma symptomen. Er was ook een relatie tussen alexithymie en slechtere astma controle en een lagere kwaliteit van leven. De suggestie dat alexithymie een patiënt gerelateerde factor is en mogelijk gerelateerd is aan ernstiger astma lijkt bevestigd te worden door de uitkomsten van de review.

Gespecialiseerde longrevalidatie

Aangezien psychologische factoren een rol kunnen spelen in de etiologie en het voortbestaan van DA, bestudeerde we de uitkomst van bestaande revalidatie behandelprogramma's die bestaan uit zowel fysieke als psychologische elementen. Gespecialiseerde gezondheidszorgpsychologen onderzochten alle patiënten en behandelden patiënten met geïndividualiseerde psychologische behandeling welke ook in een groep konden plaatsvinden. Onze studie in ***Hoofdstuk 6*** liet zien dat zo'n gespecialiseerd longrevalidatie programma kan bijdragen aan verbeterd welzijn gerelateerd aan de medische conditie in patiënten met DA en dat deze verbetering bleef op de lange termijn, dat wil zeggen 12 maanden na de revalidatie. Welzijn gerelateerd aan de medische conditie verbeterde significant samen met de significante verbetering van psychiatrische symptomen tijdens de

revalidatie. Helaas was er geen data beschikbaar met betrekking tot mogelijke veranderingen in de frequentie van exacerbaties.
Gebaseerd op de resultaten in de ***Hoofdstukken 2*** en ***3***, waarin psychiatrische symptomen complicerende factoren leken in de behandeling van DA [7], hypothetiseerden we dat de intensiteit van de psychiatrische symptomen aan het begin van de revalidatie de uitkomst van de revalidatie negatief zou beïnvloeden. Specifiek hypothetiseerden we dat de verbetering tijdens de revalidatie kleiner zou zijn als de intensiteit van de psychiatrische symptomen hoger zou zijn aan het begin van de revalidatie. In contrast tot wat we verwachten was er geen verband tussen de intensiteit van de psychiatrische symptomen aan het begin en de vooruitgang die gemaakt werd op welzijn gerelateerd aan de medische conditie tijdens de revalidatie. Het is waarschijnlijk dat vanwege een behoorlijke hoeveelheid psychologische interventies tijdens de gespecialiseerde revalidatieprogramma's, psychiatrische symptomen goed genoeg behandeld werden om in te grijpen op de 'fysieke elementen' van het PR programma, wat het programma geschikt maakt voor patiënten met DA.

ALGEMENE DISCUSSIE

THEORETISCHE EN MOGELIJKE KLINISCHE IMPLICATIES

Aan het begin van deze thesis leek een mogelijke rol voor psychologische factoren voor de etiologie en het voortduren van DA enkel bevestigd in een kleine hoeveelheid literatuur over psychologische onderwerpen in DA. Deze thesis probeerde de bestaande literatuur over psychopathologie in DA aan te vullen en om een empirische basis te creëren voor bestaande management programma's gericht op het behandelen van DA. Het hoofddoel van deze thesis was DA beter te begrijpen vanuit een psychologisch oogpunt.
De beperkte bestaande literatuur bevestigde de aanwezigheid van een hoge intensiteit van psychiatrische symptomen in DA (***Hoofdstuk 2***). Ons empirisch onderzoek bevestigde tevens deze hoge intensiteit van psychiatrische symptomen en syndromen (***Hoofdstuk 3 en 4***). Naast angst en depressie waren er ook andere psychiatrische symptomen aanwezig in DA. Het is daarom raadzaam om het brede spectrum aan psychiatrische syndromen in DA te bestuderen. Specifiek was bijvoorbeeld de obsessief compulsieve persoonlijkheidsstoornis relatief vaak aanwezig.
Hoewel deze thesis de hoge frequentie en intensiteit van psychiatrische symptomen en syndromen in DA bevestigde, blijft de rol in de etiologie en

voortbestaan van DA onduidelijk. De relatie tussen DA en psychiatrische symptomen en syndromen is waarschijnlijk tweezijdig; DA kan resulteren in psychiatrische symptomen en syndromen en in alexithymia of vice versa. Meer onderzoek naar psychologische factoren in DA, in het bijzonder longitudinaal onderzoek waarbij ook andere psychologische factoren meegenomen worden als de volgzaamheid van patiënten, coping strategieën, sociaal economische status en minder bekende factoren als veerkracht, hechtingsstijlen- en specifiek 'path analyses' zijn nodig om een empirische basis te creëren van een theorie over psychologische factoren in de etiologie en het voortbestaan van DA. Voor toekomstig onderzoek zal het combineren van deze psychologische benadering met een somatische benadering waarschijnlijk nog meer inzicht geven in de etiologie en voortbestaan van DA. Deze thesis heeft bijgedragen aan het creëren voor zo'n empirische basis omdat we bewijs gaven dat psychiatrische symptomen en syndromen in hoge mate aanwezig zijn in DA.

De vraag of behandeling van DA ook de psychiatrische symptomen en syndromen behandelt en/of vice versa is interessant voor toekomstig klinisch onderzoek. In het algemeen is psychiatrische symptomatologie meer prevalent in vrouwen, in DA was de intensiteit even hoog in mannen als in vrouwen (***Hoofdstuk 3***). Hoewel in GINA richtlijnen het screenen van psychopathologie geadviseerd wordt in een vroeg stadium van astma, worden psychiatrische symptomen en syndromen gemakkelijk over het hoofd gezien, zelfs in zeer gespecialiseerde zorg: tot wel 80% van DA patiënten die lijdt aan een psychiatrisch syndroom was niet gediagnosticeerd tijdens de meting. Dit is waarschijnlijk vanwege de nogal dramatische somatische manifestatie van de ziekte, een definitie die gebaseerd is op farmacologische behandeling en een angst voor stigmatisering in zowel de ogen van arts als patiënt.

Psychologische factoren, dat wil zeggen psychiatrische symptomen en syndromen en alexithymie, spelen een belangrijke rol in welzijn gerelateerd aan de medische conditie in DA. Echter, onze thesis bevestigde psychiatrische symptomen niet als een complicerende factor in de succesvolle gespecialiseerde longbehandeling. Hoewel psychiatrische symptomen frequent bleken voor te komen in DA, suggereert de verbetering in welzijn gerelateerd aan de medische conditie tijdens de revalidatie dat psychiatrische symptomatologie geen contra-indicatie is voor gespecialiseerde revalidatie. Psychiatrische symptomen namen af tijdens de revalidatie. Toekomstig onderzoek zou moeten uitwijzen of dit een gevolg is van de specifieke multidisciplinaire behandeling die tevens bestond uit psychologische interventies. Het is daarnaast nog altijd onduidelijk of psychiatrische symptomen complicerende factoren zijn in niet gespecialiseerde

zorg. Dit maakt ook de rol van psychiatrische symptomen in DA twijfelachtig en dus ook de vraag naar causaliteit. Het is belangrijk om specifiek te bestuderen of psychologische interventies in gespecialiseerde longrevalidatie voorkomen dat psychiatrische symptomen interfereren met de behandeluitkomst of dat psychiatrische symptomen slechts een comorbide conditie zijn die weliswaar meer en ernstiger aanwezig zijn in DA maar de behandeling niet compliceert. Bovendien is het zo dat wanneer specifieke interventies interferentie tijdens de behandeling voorkomt, deze interventies mogelijk geïntegreerd kunnen worden in een eerdere fase van astma behandeling.

Voor de klinische praktijk is het belangrijk om te overwegen deze comorbide psychiatrische symptomen en syndromen te behandelen na of tijdens de gespecialiseerde longrevalidatie in plaats van voor de revalidatie. Behandeling van psychiatrische symptomen en syndromen kan overwogen worden na de revalidatie omdat ze geen contra-indicatie bleken te zijn. Patienten hebben wel behandeling nodig vanwege de relatie met slechter welzijn gerelateerd aan de medische conditie in DA. Hoewel er een duidelijke significante vermindering van psychiatrische symptomen was tijdens de behandeling is het bovendien onduidelijk of deze symptomen verminderd zijn tot een subklinisch niveau. Dit moet in de toekomst onderzocht worden.

Verwijzing naar makkelijk toegankelijke psychologische zorg in een vroeg stadium in de eerste lijn, zoals de POH-GGZ in Nederland, een praktijkondersteuner gespecialiseerd in geestelijke gezondheidszorg wordt alsnog geadviseerd. Echter, zodra DA is gediagnosticeerd, zou psychiatrische evaluatie zeker geïncludeerd moeten worden in de standaard medische onderzoeken van patiënten met DA. Verwijzing naar gespecialiseerde gezondheidszorgpsycholoog of psychiater wordt reeds in een vroeg stadium in de astma zorg geadviseerd, in de ziekenhuis ambulante setting en niet alleen zodra of nadat een patiënt verwezen wordt naar een gespecialiseerd longrevalidatie centrum. De onder diagnostisering en daarom onderbehandeling van zowel psychiatrische symptomen en syndromen en de mogelijke rol van alexithymie in DA zou geminimaliseerd moeten worden om zoveel mogelijk de last van patiënten met DA en hun omgeving te verminderen.

Het is waarschijnlijk vanwege de dramatische manifestatie van de astma symptomen in DA moeilijk om het verschil te zien tussen psychiatrische en astma symptomen, niet alleen voor patiënten zelf maar ook voor longartsen. Het bewust zijn van de mogelijke aanwezigheid van psychiatrische symptomen en syndromen kan professionals die met astma patiënten werken gevoelig maken om dit probleem te verhelpen. Bovendien, in ieder geval in Nederland, is er nog

steeds stigma over psychiatrische ziektes. Dit kan resulteren in de onbereidheid om psychiatrische symptomen te erkennen en te accepteren [23].

Alexithymie zou ook overwogen moeten worden in DA, aangezien dit het voor patiënten niet alleen moeilijker maakt om te differentiëren tussen emoties en lichamelijke sensaties maar ook om hun somatische en psychologische/ psychiatrische symptomen te communiceren met gezondheidszorg professionals. Alexithymie zou daarom in overweging genomen worden wanneer de gerapporteerde symptomen door DA patiënten geïnterpreteerd worden. Het communiceren van hun symptomen en het begrijpen, is moeilijker voor deze patiënten en kan het onderzoek van de klinische conditie bemoeilijken en daardoor de behandeling compliceren.
Alexithymie bleek aanwezig te zijn in een substantieel deel van patiënten met DA en kan daardoor een verklaring zijn van de klinische observatie dat DA patiënten vaak vroege waarschuwingssignalen voorafgaand aan exacerbaties niet kunnen detecteren of zich vergissen in astma symptomen en emoties en teveel symptomen rapporteren.
Als een consequentie, in ieder geval in een aantal patiënten, kan alexithymie mogelijk deels het voortbestaan van DA symptomen verklaren. Het bewustzijn van de mogelijke aanwezigheid van alexithymie door gezondheidszorgprofessionals en patiënten kan behandeling verbeteren (***Hoofdstuk 5***) door het incorporeren van (bestaande) therapieën die alexithymie behandelen. Zo'n therapeutische aanpak zou onderscheid moeten maken tussen patiënten die tekenen en symptomen van astma teveel of te weinig waarnemen. Een 'nieuw' gebied van onderzoek die de rol van alexithymie kan onderzoeken in de etiologie en behandeluitkomst van DA wordt derhalve aanbevolen. Wanneer hogere intensiteit van alexithymie aanwezig is in een patiënt met DA, is een multidisciplinaire aanpak (ambulant of in een revalidatiecentrum) mogelijk de beste setting om dit probleem te diagnosticeren en behandelen zodat psychologische en somatische factoren uit elkaar gehaald kunnen worden en de patiënt kan leren om onderscheid te maken tussen emoties en gevoelens versus astma symptomen.
Behandeling van alexithymie in astma –en specifiek in DA- kan een kans zijn in de behandeling van astma, omdat het bekend is dat alexithymie belangrijk is in de ontwikkeling en het voortbestaan van andere somatische chronische ziektes [24]. Bovendien resulteerde behandeling gericht op betere waarneming van somatische en emotionele signalen in minder symptomen [24]. Tot nog toe zijn er geen studies over de behandeling van alexithymie in astma bekend.

Wij stellen een andere benadering voor ten aanzien van het begrijpen, onderzoeken en de behandeling van astma/DA. Hoewel GINA probeert een brug te slaan tussen psyche en soma, moet er ons inziens, een meer geïntegreerde kijk op astma/DA ontwikkeld worden. Zo'n kijk zou het bewustzijn in een vroeg stadium moeten bevorderen of psychiatrische symptomen en syndromen en alexithymie aanwezig zijn in patiënten met astma/DA. Als een consequentie, zou dit moeten resulteren in verwijzing in een vroeg stadium naar een arts, psychiater of psycholoog of een combinatie van gezondheidzorgprofessionals voor adequate behandeling. Reeds in de eerste lijn, zouden alle patiënten die niet adequaat reageren op de eerste stappen in de GINA richtlijnen psychologisch onderzoek moeten krijgen door een praktijkondersteuner GGZ van de huisarts. Wanneer psychiatrische symptomen aanwezig blijken te zijn, wordt verwijzing naar een psycholoog in de eerste lijn geadviseerd met daarnaast een focus op de mogelijke aanwezigheid van alexithymie. Wanneer de patiënt niet reageert op deze (multidisciplinaire) behandeling, wordt verwijzing naar een longarts en medische psycholoog van een ziekenhuis geadviseerd voor verdere diagnostiek. Wanneer psychiatrische symptomen en alexithymie een belangrijk aspect zijn astma wordt verwijzing naar een longrevalidatiecentrum geadviseerd waar een meer geïntegreerde somatische/psychologische behandeling beschikt baar is, aangezien daar zowel de somatische aspecten als psychiatrische symptomen en syndromen en alexithymie benaderd worden.

THEORETISCHE EN PRAKTISCHE LIMITATIES

MOEILIJK TE BEHANDELEN EN MOEILIJK TE BESTUDEREN

Complicerende factoren

DA is, bij definitie, een astma subgroep die moeilijk te behandelen is. Een verklaring voor de moeilijkheid in de behandeling van DA, zoals aangetoond in deze thesis, is de mogelijke rol van psychiatrische symptomen, syndromen en alexithymie. Literatuur over psychopathologie in DA was beperkt waardoor een psychologische benadering -onderzoek naar psychiatrische symptomen, syndromen en alexithymie- ten aanzien van DA een nieuwe focus leek.

DA zelf bleek tevens een moeilijke subgroep om te bestuderen. De definitie van DA is gebaseerd op farmacologische behandeling in plaats van specifieke ziekte karakteristieken. DA is daardoor een heterogene groep die bestaat uit diverse subgroepen van patiënten met verschillende karakteristieken. Het is bijvoorbeeld twijfelachtig of NFA (near fatal asthma), een subgroep van DA, vergelijkbaar is met 'brittle asthma'- een andere subgroep. Mogelijk is DA te heterogeen. Het is

echter een groep van patiënten die huisartsen en longartsen zien in hun praktijk die een grote last vormen voor zowel hen zelf als de maatschappij. Het probleem van de heterogeniteit maakte het tevens moeilijk om behandeluitkomsten te vergelijken van de paar studies die we gevonden hebben.
Een andere complicerende factor was een nogal onbekend concept van alexithymie in zowel astma als DA. Slechts een paar studies onderzochten de rol van alexithymie in astma en geen enkele specifieke studie onderzocht alexithymie in de etiologie van DA. Bovendien rapporteerde geen enkele studie over het effect van het behandelen van alexithymie in astma of DA. De mogelijke aanwezigheid van alexithymie in astma veroorzaakte ook een specifiek probleem in het bestuderen van astma/DA. Patiënten met alexithymie hebben moeite om zowel emotionele als somatische sensaties te herkennen en deze onder woorden te brengen. Dit maakt het moeilijk om adequaat te vertrouwen op zelfrapportage meetinstrumenten ten aanzien van gevoelens en sensaties welke ook verwerkt zijn in de review studies en sommige van onze eigen studies. Daarom is het belangrijk de prevalentie van psychopathologie in astma/DA patiënten die onderzocht is met zelfrapportage instrumenten met voorzichtigheid te interpreteren. Een mogelijke manier om de misinterpretatie van psychiatrische symptomatologie te overwinnen is het gebruik van een gestandaardiseerd psychiatrisch interview. Tijdens dit interview krijgt een gezondheidszorgprofessional meer inzicht in de (hoge of lage) intensiteit van symptomen welke verklaard kunnen worden door alexithymie.
Een andere complicerende factor die genoemd moet worden en altijd –bij definitie-het onderzoek naar DA beïnvloedt, is het gebruik van corticosteroïden. Corticosteroïden zijn bekend om hun behoorlijke psychotropische bijwerkingen te hebben, zeker in chronische hoge doseringen, zoals het geval is in DA [25, 26]. De psychiatrische last is verhoogt in patiënten met ernstig prednison afhankelijk astma [25] en het gebruik van orale corticosteroïden is gerelateerd aan lager kwaliteit van leven [26]. Een mogelijk onafhankelijk effect van deze medicatie op psychiatrische stoornissen zou in overweging genomen moeten worden in toekomstige studies [27].

Sterke punten en limitaties

Deze thesis heeft verschillende sterke punten en limitaties. Een eerste sterk punt is dat we onze patiëntengroep bestudeerden met slechts beperkte exclusie criteria. Dit resulteerde echter in een heterogene groep waarbij het twijfelachtig is of de resultaten gegeneraliseerd kunnen worden naar alle DA patiënten in alle settingen. Bovendien werden patiënten met ernstige psychopathologie die

konden interfereren met de behandeling ge-excludeerd in de drie empirische studies in deze thesis. Dit beperkt tevens de generaliseerbaarheid.
Een ander sterk punt is het gebruik van goed gevalideerde instrumenten, waaronder interviews in het diagnosticeren van psychiatrische stoornissen waaronder persoonlijkheidsstoornissen.
Deze thesis bestudeerde zowel de intensiteit van de psychiatrische symptomen als de aanwezigheid van psychiatrische syndromen. Een limitatie is dat het gebruik van zelfrapportage instrumenten geresulteerd kan hebben in een bias (fout) vanwege mogelijk hoge niveaus van alexithymie in DA. De interviews toonden echter ook hoge niveaus van psychiatrische syndromen aan, suggereerden dat DA patiënten lijden aan hoge niveaus van psychiatrische symptomen wat ook gezien wordt in andere studies. Bovendien, zoals boven opgemerkt, werden patiënten met ernstige psychopathologie bij wie de psychiatrische symptomen/syndromen behandeling konden interfereren ge-excludeerd, wat ook de frequentie van psychopathologie in onze samples kon verminderen. Dit benadrukt daarom dat veel patiënten met DA lijden aan hoge niveaus van psychiatrische symptomen.
We bestudeerden de relatie tussen de intensiteit van de psychiatrische symptomen en gespecialiseerde behandeling. Helaas werden psychologische interventies geïndividualiseerd wat resulteerde in (a) niet weten of en welke interventies resulteerden in de beste uitkomsten, (b) niet weten of deze interventies ervoor zorgden dat psychiatrische symptomen daardoor niet interfereerden met de behandeluitkomst. Daarnaast combineerden we nauwelijks psychologische meetinstrumenten met somatische. In toekomstig onderzoek is het belangrijk om op beide dimensies te meten. Aangezien RCT's niet wenselijk zijn in het onderzoek van deze patiënten, kunnen single case designs meer inzicht geven in de verschillende typen DA patiënten.
Er zijn ook patiënten met DA die geen psychiatrische symptomen rapporteren of alexithymie. Het is niet duidelijk welke factoren in deze patiënten de astma compliceren. Het is daarom nodig om meer onderzoek te doen in DA naar verschillende typen DA patiënten om te onderzoeken welke interventies de voorkeur hebben bij welke patiënten. Dit kan resulteren in een meer gedifferentieerd behandelaanbod die effectiever is.

CONCLUSIES

Deze thesis voorziet in empirisch bewijs dat psychiatrische symptomen en syndromen hoog prevalent zijn en vaak niet herkend worden in DA, ongeacht sekse. Gespecialiseerde longrevalidatie is mogelijk gunstig voor patiënten met

DA met langdurende effecten op welzijn gerelateerd aan de medische conditie. Psychiatrische symptomen zijn geen contra-indicatie voor de behandeling en verbeteren tevens tijdens de revalidatie. Vroege verwijzing voor psychologisch onderzoek en behandeling wordt aanbevolen voor patiënten met DA. Alexithymie is mogelijk tevens in hoge mate aanwezig in astma en DA en behoeft meer onderzoek. Toekomstig onderzoek zou een meer geïntegreerde aanpak kunnen gebruiken waarbij zowel psychologische als somatische aspecten geïntegreerd worden.

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En nu, nu is het klaar!

Lonneke

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About the author
Over de auteur

Lonneke Kanters-Prins was born on 2 maart 1981 in Zeist. In 2000 she graduated from high school at Stedelijk Gymnasium, Johan van Oldenbarnevelt in Amersfoort. After high school she began her study biological and neurological psychology at Utrecht University where she obtained her Master's degree in 2004. She subsequently began to work for Altrecht, Centre for Psychosomatic Medicine, where she worked as a clinician and a researcher in her job as a neuropsychologist. In 2005 she worked also at the Psychodiagnostic Service of Altrecht.

From 2008-2010 she studied a post-master Health Psychology at Altrecht, Centre for Psychosomatic Medicine and RINO Groep in Utrecht. Thereupon she kept working at Altrecht and started working at Merem, asthmacentre Heideheuvel as a General Health Care Psychologist and head of the department psychology. She then started her PhD at the Tilburg University in collaboration with Utrecht University, asthmacentre Heideheuvel in Hilversum and Revant, rehabilitation centre in Breda.

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Lonneke Kanters-Prins werd geboren op 2 maart 1981 te Zeist. In 2000 behaalde ze haar VWO diploma aan het Stedelijk Gymnasium, Johan van Oldenbarnevelt in Amersfoort. Na het gymnasium begon ze met haar studie biologische en neuropsychologie aan de Universiteit Utrecht waar ze in 2004 haar doctoraal behaalde. Na haar studie is ze in 2004 gaan werken bij Altrecht, Centrum Psychosomatiek voorheen Eikenboom waar ze zowel klinische als onderzoekswerkzaamheden uitvoerde als neuropsycholoog. Daarnaast heeft ze in 2005 een jaar gewerkt bij de Psychodiagnostische Dienst van Altrecht. Van 2008-2010 volbracht ze de GZ-opleiding bij Altrecht, Centrum Psychosomatiek voorheen Eikenboom en de RINO Groep te Utrecht. Lonneke is vervolgens zowel bij Eikenboom blijven werken en gaan werken bij Merem, behandelcentrum Heideheuvel, een gespecialiseerd astmacentrum. Hier werkte zij als GZ-psycholoog en vakgroepcoördinator van de afdeling psychologie. Naast haar werkzaamheden als clinicus begon ze met haar promotietraject aan de Universiteit van Tilburg in samenwerking met zowel de Universiteit van Utrecht, Heideheuvel als Revant, voorheen Schoondonck, revalidatiecentrum te Breda.
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